COMPARISON OF MUSCLE DENSITY, SIZE, STRENGTH, AND FUNCTIONAL MOBILITY BETWEEN FEMALE FALLERS AND NON-FALLERS

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ABSTRACT

Imaging based muscle density (MD) is associated with poor lower extremity performance, the development of mobility impairments, frailty, and hip fracture. These associations are all related to falls, yet no studies have investigated MD in community dwelling fallers. The primary objective of this study was to determine whether lower leg MD differed between community dwelling elderly women who do and do not report falls. The secondary objective was to determine if lower leg muscle cross sectional area (MCSA), timed up & go (TUG) test, and relative grip strength (RGS; as a ratio to body mass) differed between fallers and non-fallers. Women (N = 135), 60 years or older (mean age 74.1, SD 7.6) were recruited from a random sample of Saskatoon residents. Fallers (n = 36) and Non-fallers (n = 99) were grouped based on 12-month retrospective falls survey response. A peripheral quantitative computed tomography (pQCT) scan of the non-dominant lower leg was acquired to determine MD and MCSA. Participant age, height, weight, TUG test result and RGS were recorded. Between-group differences in mean age, body mass index (BMI), MD, MCSA, TUG and RGS were compared using independent t-tests ($P < 0.05$). MD and TUG results were transformed to meet the assumption of normality for parametric analysis. Age, BMI, MCSA and RGS did not differ ($P > 0.5$). Fallers had 3.2% lower MD ($P = 0.01$) and 15.1% slower TUG scores ($P = 0.02$), than non-fallers. Muscle density may serve as a physiological marker for the assessment of muscular health and fall risk in community dwelling elderly women.

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"The road of life twists and turns and no two directions are ever the same. Yet our lessons come from the journey, not the destination."

– Don Williams Jr., American Novelist and Poet (1968 -)

Many great adventures begin when life requires one to set out into the unknown. I am grateful to be able to reflect on my road travelled with exultancy; not only for the culmination of my learning, but for the journey itself, and the paths which now lay before me. The pursuit of my Masters Degree has been a stimulating experience, due largely to the involvement of wonderful and committed characters whose influence I feel compelled to recognize.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index (kg/m^2)
CaMos	Canadian Multi-centre Osteoporosis Study
CT	Computed Tomography
F	Faller
HU	Hounsfield Units
NF	Non-Faller
MCSA	Muscle Cross Sectional Area (cm^2)
MD	Muscle Density (mg/cm^3)
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
pQCT	Peripheral Quantitative Computed Tomography
RGS	Relative Grip Strength (kg/kg)
TUG	Timed Up and Go (s)
U of S	University of Saskatchewan

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INTRODUCTION

Falls are a major public health concern in the elderly. Approximately 30% of community dwelling elders fall each year, and 12% experience recurrent falls (O'Loughlin, Robitaille et al. 1993). The consequences of falling, such as injury, hospitalization, loss of independence, and morbidity, are devastating to the individual and for society (Rubenstein & Josephson 2002). The socio-economic burden of falls totals 1.5% of all health care costs in the western world (Heinrich, Rapp et al. 2009). The need for prudent fall prevention is accentuated by age-adjusted data suggesting that the rate of fall-induced injury in older persons is increasing (Kannus, Parkkari et al. 1999; Hartholt, van der Velde, et al. 2010). Physical activity and exercise strategies aiming to increase strength, balance, flexibility or endurance are effective in reducing the number of persons who fall, and the overall number of falls (Gillespie, Robertson et al. 2009). Muscle function is a factor in fall incidence, and muscular strength and power are potential candidates for preventative exercise interventions (Rubenstein, Josephson et al. 2000; Ferri, Scaglioni et al. 2003; Moreland, Richardson et al. 2004 Faber, Bosscher et al. 2006; Horlings, van Engelen et al. 2008). The strength and power of dorsiflexor and plantarflexor muscles in the lower leg are important determinants of fall incidence (Wolfson, Judge et al. 1995; Takazawa, Arisawa et al. 2003; Moreland, Richardson et al. 2004; Perry, Carville et al. 2007). Declines in the performance of these muscles with advancing age appear to be due to intrinsic changes in the muscle tissue (Goodpaster, Carlson et al. 2001), rather

than neurological activation or antagonist muscle involvement (Ochala, Lambertz et al. 2004; Simoneau, Martin et al. 2005).

Imaging technologies such as peripheral quantitative computed tomography (pQCT) may provide insight into the morphology of these muscles. Imaging studies have revealed that increases in intramuscular fat and non-contractile tissues are associated with lower tissue density (Goodpaster, Kelley et al. 2000) and muscle cross sectional area (MCSA) in the plantarflexors and dorsiflexors of older individuals (Rice, Cunningham et al. 1989; Kent-Braun, Ng et al. 2000). Muscle tissue density and MCSA of the lower leg muscles have been studied with pQCT in both men and women with Frailty Syndrome, a condition that is highly associated with both ageing and falling (Cesari, Leeuwenburgh et al. 2006). Frailty was significantly ($P < 0.001$) and inversely related to pQCT derived MD (r = -0.215) and MCSA (r = -0.186) in this study (Cesari, Leeuwenburgh et al. 2006). Furthermore, a recent randomized controlled trial demonstrated that a targeted physical activity regimen was capable of maintaining muscular strength and preventing decreases in muscle tissue density in the elderly (Goodpaster, Chomentowski et al. 2008).

However, no currently available literature specifically assesses the muscle density of the lower leg in fallers and non-fallers. The TUG test and hand grip strength assessment are reported to distinguish fallers (Gunter, White et al. 2000; Shumway-Cook, Brauer, et al 2000; Pijnappels, van der Burg et al 2008), individuals with functional mobility impairments (Rantanen, Guralnik, et al. 1999;

Lauretani, Russo et al 2003; Moreland, Richardson et al. 2004; Yelnik & Bonan 2008), and disability (Warburton, Gledhill et al 2001; Bohannon 2008). Therefore my thesis aims to determine if differences exist in pQCT-derived lower leg MD, and MCSA, as well as TUG test score and handgrip strength between fallers and non-fallers.

1.0 REVIEW OF LITERATURE

To provide the knowledge framework essential for conducting this project, this chapter presents the key concepts of falls, muscle physiology, and the muscle measurement techniques utilized in my thesis. Current evidence of the physiological changes that occur in muscle with age will be included, with emphasis on the lower leg.

1.1 Falls: A Common Health Concern in Older Age

In Canada approximately 30% of community dwelling elders (≥65 yrs of age [WHO 1984]) fall each year, and 12% experience multiple falls (O'Loughlin, Robitaille et al. 1993). Studies in other industrialized populations have reported similar fall rates of 28 – 35% of persons over 65, with an increase to 32 - 42% of persons 75 and older (Masud & Morris 2001). Women are more likely to experience a fall, and even well functioning older persons are not immune to fall events (de Rekeneire, Visser et al. 2003). The experience of a fall can be a cruel event; with consequences that can include serious injury, hospitalization, fear, a loss of independence, and morbidity (Rubenstein & Josephson 2002). Almost one quarter of fall events result in serious injury, half of fallers report developing a fear of falling, and a quarter of fallers restrict their activities (shopping, household chores, physical activity) due to this fear (Tinetti, Speechley, et al. 1988; Tinetti & Williams 1998). A recent systematic review of falls and their associated costs in the western world estimated the societal burden of falls to account for 1.5% of all health care costs, with the average cost of a single fall ranging from $2,044 to

$25,955 USD (Heinrich, Rapp et al. 2009). There is concern that these costs will rise at a greater rate than the growth of the elderly population. Age-adjusted data suggests that the rate of fall-induced injury in older persons is increasing (Kannus, Parkkari et al. 1999), with an annual fall incidence increase of 1.3% for men and 0.7% for women over the last 27 years (Hartholt, van der Velde, et al. 2010). While the case has been made that falls are prevalent and costly (for both the victims and society), how fall data are collected is fundamental in our understanding of these events.

1.1.1 Falls: A Definition and Data Collection

How a fall event is defined and interpreted will influence the occurrence of falling reported by seniors. Many studies have defined falls differently, some with broad definitions and others with definitions intrinsically or environmentally narrowed to exclude falls that occur due to specific events (syncope, violence, car accidents, sports, etc.) (Masud & Morris 2001). Surprisingly, it was not until recently that fall definition consensus was established and published by the European Prevention of Falls Network (Lamb, Jørstad-Stein et al. 2005). According to their consensus statement, a fall is broadly defined as “any event where any part of your body unexpectedly contacted the ground or another lower surface”. Adherence to this consensus definition is important for the assembly of comparable fall data, which will further enhance fall research and health policy (Hauer, Lamb, et al. 2006).

Many fall studies have collected retrospective data on falls incidence (Gunter, White, et al 2000; de Rekeneire, Visser et al. 2003; Hauer, Lamb et al.

2006; Langsetmo, Hanley et al. 2008), primarily for the convenience of collecting a high volume of falls information in a very short span of time. Prospective methodologies are more resource intensive and may include daily record keeping of falls, with weekly or monthly telephone follow-ups (Hauer, Lamb et al. 2006). While the reliability of a retrospective recall in an elderly population is of concern, data from a longitudinal prospective fall monitoring study demonstrated that only 13% of elderly men and women failed to recall a fall event in the last 12 months (Cummings, Nevitt et al. 1988), whereas short-term recall was worse (32% and 26%) at 3 and 6 months respectively. Unfortunately the effect of participation in this prospective study could not be controlled for, and these recall percentages likely reflect an overestimation of recall ability.

1.1.2 Falls: Risk Factors

Risk factors are variables that may increase the likelihood of experiencing a harmful event (Kannel & Schatzkin 1984). The identification and monitoring of these factors is an important aspect of fall prevention research. Falls can be complex occurrences; they can be influenced by many risk factors, and a single fall could be due to one or a combination of these factors (Rubenstein 2006). Rubenstein & Josephson published a summary of 16 controlled studies that examined multiple risk factors in community dwelling and institutionalized elderly persons. Fall risk factors among these studies included muscle weakness, a previous history of falls, gait deficits, balance deficits, use of an assistive device, visual deficits, arthritis, impaired activities of daily living, depression, cognitive

impairment, and age (American Geriatrics Society (AGS), British Geriatrics Society (BGS), et al 2001; Rubenstein & Josephson 2002). Muscle weakness was a significant risk factor in 10 of 11 studies that measured muscle strength. A meta-analysis of these studies revealed that elderly persons with muscle weakness were 4.4 times more likely to fall than their fit peers (AGS, BGS et al. 2001; Rubenstein & Josephson 2002). Muscle weakness presented the largest relative risk (4.4) for falls, and gait and balance deficits produced a mean relative risk of 2.9 (AGS, BGS, et al. 2001; Rubenstein & Josephson 2002). These important factors appear to be inter-related (Wolfson, Judge, et al. 1995; Butler, Lord, et al. 2008). Lower limb muscle weakness is apparent in persons who display poor balance, abnormal gait, and reduced mobility (Lord & Sturnieks 2005; Butler, Lord, et al. 2008). In a prospective meta-analysis of muscle weakness and falls, the presence of lower extremity weakness almost doubled the odds of having a fall (OR 1.76 [1.31 – 2.37]) (Moreland, Richardson, et al. 2004). In both meta-analyses muscle strength was assessed indirectly using functional testing outcomes or directly by measuring strength or power. Furthermore, community dwelling and institutionalized elderly population studies were analyzed together. This is relevant because muscle weakness, balance, and gait abnormalities are much more pronounced in institutionalized elderly fallers (Wolfson, Judge, et al. 1995; Takazawa, Arisawa et al. 2003). However, muscle weakness, balance, and gait abnormalities are also known to influence fall susceptibility in the community dwelling elderly population (Tinetti, Speechley,

et al. 1988; Gehlson, Whaley, et al. 1990; Lord, Ward, et al. 1994; Vellas, Wayne, et al. 1998). Therefore it is likely that the mean relative risks and odds ratios of falling calculated by Rubenstein & Josephson, and Moreland, Richardson et al. may overestimate the relative risks in community dwelling individuals.

Almost one in five falls (17%) are believed to be caused by muscle weakness or gait and balance disorders, which are second only to environmental hazards (31%) as the primary cause of falls (Rubenstein & Josephson 2002). In light of the importance of these inter-related risk factors, several exercise interventions have attempted to improve lower body and postural strength, balance, flexibility and endurance in the elderly (Gillespie, Robertson et al. 2009). While environmental hazards are an important cause of falls, a recent meta-analysis of randomized controlled fall prevention trials concluded that home safety interventions were generally not effective for fall prevention (Gillespie, Robertson et al. 2009). Furthermore, physical activity and functional weight bearing exercises were reported to be effective in reducing the number of fallers, and the rate of falling (Gillespie, Robertson et al. 2009). These results highlight the importance of carefully managed exercise programs, which target the risk factor of muscle weakness, as an efficacious avenue to reduce the overall risk of falls.

1.2 Skeletal Muscle

Skeletal muscle tissue provides us with the essential function of movement, allowing us to interact, survive, and thrive in the world around us. While its

healthy function often goes underappreciated, declines in muscle health with age or diseased states can lead to locomotor instability or failure, and have dire consequences such as falls, injury, and loss of independence (Warburton, Glendhill, et al. 2001a). To better comprehend the changes that occur with ageing as well as their implications an introduction to muscle structure and function is necessary.

1.2.1 Basic Muscle Structure and Function

Skeletal muscle tissue is organized into distinct muscles, which perform lengthening, shortening, and stabilizing contractions across the joints of the body (McComas 1996). Muscle tendons form a musculo-skeletal junction which transfers contractile forces generated by the muscle's cells to its origin and insertion points on the skeleton (Lieber 2010). This musculo-tendinous unit is composed of many muscle fascicles bound together in a connective tissue fascia that tapers into a tendon. Each muscle fascicle is a bundle of muscle fibres enclosed in a sheath of connective tissue. While each fascicle spans the entire length of a muscle, each individual fibre within the fascicle may not (Lieber 2010).

The muscle fibre is the basic cellular unit of muscle and is highly specialized to facilitate muscular contraction (McComas 1996). Maintenance of an energy supply within each muscle fibre is important for muscular performance. To help accommodate the metabolic requirements involved in muscular contraction, each muscle fibre's cytoplasm is densely packed with mitochondria to metabolize glucose and lipids into adenosine triphosphate for cellular fuel

(McComas 1996). As a convention of this metabolic pathway, cytoplasmic quantities of glycogen and lipid (known as intramyocellular or intramuscular fat), are stored in proximity to the mitochondria within the muscle fibre (Lieber 2010). Stores of intermuscular fat also exist, between the fibres and fascicles (Kuk, Saunders, et al. 2009). However, relative to other depots in the body muscular lipid storage is usually minimal, existing as an ancillary muscle fuel source to conserve glycogen (Lieber 2010). In healthy muscles the relative amount of mitochondria and intramyocellular fat within a muscle fibre increases with a fibre's reliance on oxidative metabolism (Lieber 2010).

Muscle fibres are organized into motor units by innervation with a common α-motoneuron. Alpha-motoneurons link muscle fibres to the central nervous system and coordinate the forces generated (McComas 1996). Motor units tend to consist of similar fibre types, interspersed among the fibres of other motor units within a muscle (Lieber 2010). The complex coordination of these motor units across multiple muscle groups is necessary for the successful completion of the typical activities of daily living (Patterson, Jones et al 2007).

The functional status or functional capacity of a muscle (or a group of muscles), is a fitness measure determined by an ability to perform the tasks and necessary activities of daily living (Warburton, Gledhill, et al 2001b; Starfield 2001). Strength, power, and endurance capacity are parameters of muscle functional capacity. A decline in any one of these can affect an individual's success in performing activities of daily living and lead to a loss of independence

or disability (Warburton, Gledhill, et al 2001b; Patterson, Jones et al 2007). Muscle strength is considered to be the maximum torque generated by a muscle exerting a force on a moment arm at a specific velocity (Puthoff, Janz, et al. 2008). Muscle power is a product of both the force and the velocity with which the force is applied (Bean, Leveille et al 2003). Both strength and power are influenced by muscular, tendinous, nervous and skeletal factors (Lieber 2010; Lang, Streeper, et al. 2010). Endurance reflects a muscle's capacity to sustain a given force or power output, and may be influenced by cardiovascular factors in addition to the factors that affect strength and power (Patterson, Jones et al 2007). In older persons, functional muscle capacity is often assessed using tests designed to mimic activities of daily living (Moreland, Richardson et al. 2004). Examples include tests that assess a persons' ability to stand from a chair, climb stairs or walk a certain distance (Waburton, Gledhill, et al. 2001b; Moreland, Richardson et al. 2004).

Now that I have introduced the basics of muscle structure and function, age expedited muscular changes and their implications can be fully appreciated. These changes are of primary concern for the elderly population as they can result in functional limitations, which impact their quality of life and general well being.

1.2.2 Muscle Ageing

Factors such as lifestyle, nutrition, and disease may have negative effects on muscular capacity, however age associated changes in muscle structure and

function are the primary contributors to decline (Lieber 2010). The ageing of the neuromuscular system is reflected in the intrinsic changes that occur in muscle tissue (Vandervoort & McComas 1986). These changes are characterized by a decrease in overall MCSA (Frontera, Hughes et al. 2000; Goodpaster, Carlson et al. 2001) number of motor units (Porter, Vandervoort et al. 1995; Lieber 2010), muscle fibre number and size (Vandervoort 2002; Lee, Cheung et al. 2006).

An absolute decline in muscle strength becomes most pronounced in the years following the sixth decade of life with losses of 1 – 1.5 % per annum reported in otherwise healthy adults (Skelton, Greig et al. 1994; Vandervoort 2002; Faulkner, Larkin et al. 2007). Relative to young adults this decline eventually results in a 20 to 40% reduction in voluntary isometric strength by the seventh or eighth decade of life. Some evidence suggests that the lower body may experience greater declines in muscle mass, thickness, and strength with age (Lynch, Metter, et al. 1999; Janssen, Heymsfield, et al. 2000; Candow & Chilibeck 2005). Also, the decline in the rate of force generation appears to be most marked on the distal muscles of the leg (Vandervoort 2002). These muscles include the dorsiflexors, evertors, and the powerful plantar flexors of the foot. In young, healthy men and women the plantar flexor muscles of the lower leg are composed of a slower, more oxidative fibre types. The Gastrocnemius are approximately 60% slow twitch muscle fibre, and the soleus 80% (Gollnick, Sjödin, et al. 1974). Therefore the contraction velocity, force, and power output of

these muscles may be greatly affected by age related declines in fast twitch fibre types.

Declines in muscle power are reported to be 25% greater than declines in strength (Patterson, Jones et al 2007). The importance of muscle power is especially pronounced in tasks which require high velocities of movement, such as preventing and recovering balance from a trip (Wolfson, Judge et al. 1995; Thelen, Schultz et al. 1996; Van Dieen, Pijnappels, et al. 2005). Therefore, it is not surprising to find that the strength and power abilities of dorsiflexor and plantarflexor muscles in the lower leg are known to be important determinants of fall incidence (Wolfson, Judge et al. 1995; Suzuki, Bean, et al. 2001; Takazawa, Arisawa et al. 2003; Bean, Leveillie, et al 2003; Moreland, Richardson, et al. 2004; Perry, Carville et al. 2007; Pijnappels, van der Burg et al 2008).

Furthermore, age related increases in non-contractile tissues and inter and intramuscular fat are well documented (Rice, Cunningham, et al. 1989; Kent-Braun, Ng et al. 2000; Goodpaster, Carlson et al. 2001; Delmonico, Harris, et al 2009; Schwenzer, Martirosian et al. 2009; Kuk, Saunders, et al. 2009). In the next section I will summarize the evidence related to inter and intramuscular fat and ageing.

1.2.3 Ageing and Muscle Adiposity

The increases in inter and intramuscular fat observed with age are not well understood. Metabolic hypotheses speculate that an increase in ectopic storage in both visceral and muscular sites is a result of a diminished ability in

subcutaneous fat depots to regulate fatty acids in the blood stream (Despres & Lemieux 2006; Kuk, Saunders, et al. 2009). Cross-sectional studies also suggest that muscular fat is associated with anemia, diabetes, insulin resistance, and obesity (Cesari, Penninx et al. 2004; Miljkovic, Wang et al. 2008; Kuk, Saunders, et al. 2009; Miljkovic & Zmuda 2010; Marcus, Addison et al. 2010).

The ageing trend toward a more oxidative fibre type composition (Vandervoort 2002; Lang, Streeper, et al. 2010) may also play a role in this observed increase. Larger, more glycolytic muscle fibres are particularly susceptible to motoneuron denervation and atrophy (Porter, Vandervoort et al. 1995; Vandervoort 2002; Faulkner, Larkin et al. 2007). Lower leg pQCT derived muscle density (as a surrogate of muscular fat deposition; described in section 1.3.4) is reported to be associated with indicators of muscle fibre denervation as a result of α-motoneuron axon loss (Lauretani, Bandinelli, et al. 2006).

While the direct causes of the increased muscular fat deposition observed with age are not yet elucidated, recent CT research concerning this trend and concomitant changes in muscular performance is particularly intriguing (Marcus, Addison et al. 2010). In women thigh muscle attenuation (a CT- based gauge of muscular fat deposition; described in section 1.3.4) has proven to be a predictor of specific muscle torque ($R^2 = 0.05$, $P < 0.0001$), independent of the size of intermuscular and subcutaneous fat depots (Goodpaster, Carlson et al. 2001). Prospective CT data in elderly men and women highlighted the long-term effects of elevated muscular fat deposition (Visser, Goodpaster, et al. 2005). Persons in

the lowest quartile of muscle attenuation were reported to be 50 – 80% more likely to develop difficulties walking a quarter mile or climbing ten stairs without rest, independent of baseline MCSA and strength (Visser, Goodpaster, et al. 2005). It has also been reported that decreased thigh, and pelvic muscle attenuation increases the risk of hip fracture, even after accounting for bone mineral density (Lang, Koyama et al. 2008; Lang, Cauley et al 2010). Over 90% of hip fractures are reported to be the result of a fall (Parkkari, Kannus et al. 1999).

The effects of elevated inter and intramuscular fat deposition was further investigated using functional performance testing by Visser et al. (2002). Their study found that increased muscle fat deposition was associated with decreased lower extremity performance (defined as a 6m timed walk score and a timed 5 repetition sit to stand score) in women ($r = 0.193$) and men ($r = 0.292$). These associations were adjusted for total body fat, education, health status, and lifestyle variables but remained statistically significant ($P < 0.01$) and independent of the amount of muscle at the mid-thigh (Visser, Kritchevsky, et al. 2002). Furthermore an RCT including a targeted physical activity regimen reportedly maintained muscular strength and prevented age related decreases in muscle tissue attenuation in the elderly (Goodpaster, Chomentowski et al. 2008). Even more recently, a progressive resistance training intervention in men and women (65 – 83 yrs) demonstrated significant ($P < 0.001$) concomitant changes in thigh muscle attenuation and muscle strength with detraining (-7.7 ± 1.0% HU, -17.6 ±

1.3% Kg), as well as increases with retraining (+5.4 ± 0.5% HU, +19.8 ± 2.0% Kg) (Taaffe, Henwood, et al. 2009).

1.3 Measuring Muscle Properties in Fallers

The following measures were included in my study for the relevant data they provide, as well as their practical utility and convenience. A description of each measure as well as their advantages and disadvantages follows.

1.3.1 Functional Tests: Grip Strength

Isometric handgrip strength is considered an easy, reliable and inexpensive surrogate of overall muscle strength (Rantanen, Era et al. 1994; Lauretani, Russo et al. 2003; Moreland, Richardson et al. 2004; Sallinen, Stenhold el al. 2010). It is commonly measured using a hand-held isometric handgrip dynamometer (Bohannon, Peolsson et al. 2006). Clinical guidelines specify a seated position with the arm supported, elbow at 90° and forearm in neutral (Fess 1992), however they are not always adhered to (Bohannon, Peolsson et al. 2006). The participant maximally contracts their hand, squeezing the device for 3-5 seconds (Fess 1992). Handgrip strength has been found to be moderately associated with other muscle groups as well as muscle function, and has discriminating value in the identification of fallers and persons with mobility impairments (Rantanen, Era et al. 1994; Lauretani, Russo et al. 2003; Moreland, Richardson et al. 2004; Pijnappels, van der Burg et al 2008). Associations include lower extremity isometric strength ($r = 0.70$, *P = N.R.*) (Lauretani, Russo et al. 2003), the rate of plantarflexor and knee extensor torque development ($r = 0.51$; 0.78, $P < 0.05$;

0.01), maximum knee extensor torque and maximum leg press force (r = 0.71; 0.59, $P < 0.01$; 0.05), and maximum vertical jump height (r = 0.69, $P < 0.01$) (Pijnappels, van der Burg et al 2008). As such, low handgrip strength as an indicator of muscle weakness is an intrinsic risk factor for falling (AGS, BGS, et al. 2001; Moreland, Richardson et al. 2004) and has been suggested as a screening tool for persons at increased risk of physical disability in old age (Rantanen, Guralnik et al. 1999) and age associated muscle loss (Lauretani, Russo et al. 2003).

1.3.2 Functional Tests: Timed Up and Go

The Timed Up and Go test is a simple and common tool recommended to clinically assess anyone who has experienced a fall (AGS, BGS et al. 2001; Yelnik & Bonan 2008). To perform this test participants are asked to stand up from a seated position in a chair, walk three meters at their normal walking pace and then return to the chair at the same pace and sit back down (Yelnik & Bonan 2008). Shorter test times are desirable (Podsiadlo 1991). TUG times are significantly correlated with mobility (r = -0.31, $P < 0.001$), reduced lower extremity power (r = 0.42, $P < 0.001$), knee extension strength (r = -0.19, $P <$ 0.05), proprioceptive deficiencies (r = 0.26, $p < 0.005$) and increased postural sway (r = 0.31, $P < 0.001$) (Gunter, White et al. 2000; Whitney, Lord, et al. 2005). Most of the literature regarding TUG suggests it to be a worthy clinical tool for the identification of fallers and the prediction of falls (Gunter, White et al. 2000; Shumway-Cook, Brauer et al. 2000; Lin, Hwang, et al. 2004), however its ability

to identify female fallers has recently come into question (Thrane, Joakimsen, et al. 2007). Regardless, the test is a validated and reliable descriptive measure of functional mobility, providing information about participant balance, gait speed, and functional ability (Podsiadlo D 1991; Gunter, White et al. 2000; Lin, Hwang, et al. 2004; Whitney, Lord, et al. 2005; Yelnik & Bonan 2008).

1.3.3 Size Based Strength Estimates: Muscle Cross Sectional Area

MCSA is a commonly utilized in vivo measure of a muscle's anatomical cross sectional area, which is correlated with a muscle's maximum voluntary contraction forces (Bamman, Newcomer et al. 1999). MCSA provides a useful indication of contractile area, and lower leg MCSA is approximately 20% smaller in older adults (Narici, Maganaris et al. 2003; Morse, Thom et al. 2005). As a surrogate of muscle force, MCSA does not account for muscle fibre pennation angle, a quality that is known to differ with muscle fitness and age (Aagaard, Andersen, et al. 2001; Narici, Maganaris et al. 2003). However, the degree of pennation is often inconsequential and unlikely to have a large influence on anatomical cross section based estimates of muscle force (Lieber 2010). This was reflected by Bamman et al. who demonstrated adequate precision in MCSA estimates of plantar flexor muscle specific tension in the lower legs of pre-menopausal women (Bamman, Newcomer et al. 1999). Accounting for muscle fibre pennation angles did not offer better precision in this population (Bamman, Newcomer et al. 1999).

Age related decreases in MCSA, may not directly account for the decline in lower leg muscle torque in older adults (Lauretani, Russo, et al. 2003, Runge, Rittweger, et al. 2004; Reeves, Narici, Maganaris 2006). Depending on the imaging method utilized, MCSA can include non-contractile components of the muscle (vasculature, inter and intramuscular fat, connective tissue), and as such is limited as an estimate of a muscle's potential. Increases in non-contractile muscle material are well documented with age (Rice, Cunningham, et al. 1989; Kent-Braun, Ng et al. 2000; Goodpaster, Carlson et al. 2001; Delmonico, Harris, et al. 2009; Schwenzer, Martirosian et al. 2009). These compositional changes could lead to overestimations of the actual plantar flexor and dorsiflexor muscle contractile area in older populations (Reeves, Narici, Maganaris 2006).

1.3.4 Tools for Assessing Adiposity: Muscle Imaging

The linear attenuation properties of each tissue in the human body can influence x-ray energies passing through it (Adams 2009). CT scanners utilize this principle to measure the absorption profile of biological tissues (Stratec 2008; Lang 2010). A Hounsfield Unit (HU) scale is used to represent the attenuation properties of tissues scanned. Relative to water (0 HU) fat tissue is characterized by negative attenuation, while muscle tissue is positive (Hounsfield 1980; Goodpaster, Kelley et al. 2000; Adams 2009).

Goodpaster et al. validated CT derived muscle attenuation for the detection and quantification of fat content in muscle. A near perfect linear decline in emulsion phantom attenuation was observed (-1 HU for every 1g increase of

lipid in 100ml of solution). Muscle attenuation differed ($P < 0.01$) between lean and obese, as well as lean and diabetic groups, and was correlated (r = -0.58, $P = 0.019$) with the triglyceride content of vastus lateralis muscle biopsies. Muscle attenuation also demonstrated good concordance within (CV = 3.3%) and across (r = 0.60 to 0.77, $P < 0.01$) thigh, lower leg, hip, and spine muscle groups. Precision (CV%) for muscle attenuation of the lower leg was 0.85% (Goodpaster, Kelley et al. 2000). In support of these accounts by Goodpaster et al., CT muscle attenuation has been cross validated with MRI, the current medical imaging "gold standard" for body composition. Magnetic resonance spectroscopy (MRS) is an advanced MRI technique that is better able to distinguish inter and intramuscular fat (Miljkovic & Zmuda 2010). Lower leg muscle attenuation is well correlated (r = 0.87, $P < 0.01$) with MRS estimates of intramuscular lipid content in the soleus muscle (Larson-meyer, Smith et al. 2006). The utilization of CT derived muscle attenuation in muscle research was previously summarized in Section 1.2.3 "Ageing and Muscle Adiposity". The remainder of this section will focus exclusively on Peripheral Quantitative Computed Tomography (pQCT), and its utility in the study of muscle.

Peripheral quantitative computed tomography is an inclusive term for any quantitative CT assessment in the periphery of the skeleton. However, in the literature "pQCT" is typically reserved for compact dedicated scanners (Prevrhal, Engelke, et al. 2008) and I will only refer to the dedicated scanners in this thesis. The primary use of pQCT is to provide information on bone tissue distribution and

structure in the forearm and lower leg (Prevrhal, Engelke, et al. 2008). Relative to whole body CT devices, pQCT scanners are more compact, cost-effective, and expose participants to substantially lower effective doses of radiation (Engelke, Adams et al. 2007). With the exception of Single Photon Absorptiometry, pQCT emits the lowest effective dose of all densitometric techniques (Guglielmi, Schneider, et al. 1997).

The Stratec XCT 2000 pQCT in our lab was factory calibrated to the European Forearm Phantom, which consisted of a water equivalent soft tissue simulating material (Guglielmi, Schneider, et al. 1997; Augat, Gordon et al. 1998; Stratec 2005). Thus, contrary to CT attenuation (HU), pQCT quantifies all tissues in terms of volumetric bone mineral density (vBMD), measured in milligrams of calcium per cubic centimeter (mg/cm^3), calibrated with fat equal to 0 mg/cm^3 and a resin based water equivalent material as 60 mg/cm^3 (Augat, Gordon et al. 1998; Stratec 2005; Adams 2009). Similar to a full body CT scanner, pQCT is also able to exploit differences between fat, muscle, and bone to determine MD, and MCSA. pQCT is limited to scanning the arms and legs, and is not able to distinguish individual muscles. Thus, pQCT derived lower leg and forearm MD and MCSA provide global measures of appendicular muscle (**Figure 1.1)**.

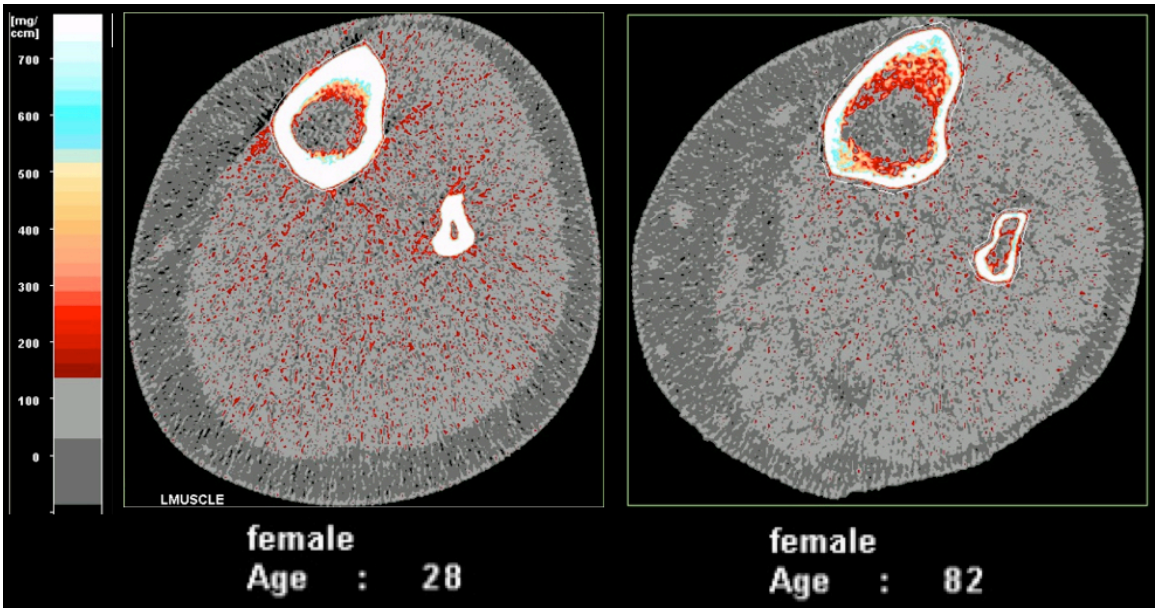


Figure 1.1: A young and old comparison of pQCT scans of the lower leg. Tissues are displayed according to their density (mg/cm^3). Scanner resolution is not able to ascertain individual muscles, however overall MCSA and MD can be determined.

The precision (CV%) for pQCT derived lower leg MCSA is reported to be between 1.4 and 2.9% (Swinford & Warden 2010; Lorbergs, Jackowski et al. 2008) and it has been extensively studied as a surrogate of lower leg muscle size and function (Rittweger, Beller et al. 2000; Lauretani, Russo et al. 2003; Runge, Rittweger et al. 2004; Cesari, Leeuwenburgh et al. 2006; Lauretani, bandinelli, et al. 2006; Rittweger & Felsenberg 2009).

Contrary to pQCT derived MCSA, the application of pQCT derived lower leg MD is still relatively new and understudied. A few studies have made use of MD as a gauge of general muscle tissue adiposity, demonstrating a relationship with anemia (Cesari, Penninx et al. 2004), frailty (Cesari, Leeuwenburgh et al. 2006) motor neuron reductions (Lauretani, Bandinelli, et al. 2006) and diabetes (Miljkovic-Gacic, Wang et al. 2008). Considering the aforementioned CT derived

muscle attenuation literature, and the cost and safety advantages of conducting pQCT research, the relevance of a pQCT derived lower leg MD variable warrants further investigation. The precision (CV%) of the XCT2000 derived lower leg MD measured in a convenience sample of college students is reported to be 0.6% (Swinford & Warden 2010). However, precision of this measure has not been reported in an elderly population.

1.4 Summary

To summarize, falls are a serious health concern in the elderly, and the health care burden associated with falls has been increasing. Decreased muscle function, particularly in the muscles of the lower leg has been identified as a major contributing factor to the occurrence of falls in the elderly. Grip strength measures and the TUG test are common and convenient tools used to functionally assess fall risk as well as overall and lower body muscular performance. Imaging based MCSA provides a precise measure of muscle size, and also serves as a known surrogate of muscle force. Furthermore CT and pQCT research has identified muscle attenuation and muscle density as a gauge of muscular adiposity, which increases with age, and appears to be connected to muscle function in the elderly. Relative to CT, pQCT is a more cost effective imaging alternative for the arms and legs, and provides lower levels of radiation exposure. No studies currently exist which directly compare measures of CT derived muscle attenuation or pQCT derived lower leg muscle density with the occurrence of falls, presenting a relevant gap in the literature. Therefore I plan to

investigate this muscle variable in community dwelling elderly women who do and do not report falls, to determine whether or not differences in MD exist. The results of this preliminary investigation may reveal a new aspect of the underlying muscle pathologies associated with falls in old age.

2.0 OBJECTIVES

2.1 Primary objective:

To determine whether there is a significant difference in pQCT derived MD between groups of community dwelling elderly women who do and do not report falls.

2.2 Secondary objectives:

To investigate whether there are any significant differences in pQCT derived MCSA, TUG test score and RGS between groups of community dwelling elderly women who do and do not report falls.

3.0 HYPOTHESIS

After accounting for any significant differences in age and BMI, I hypothesize that pQCT derived lower leg MD, MCSA, TUG test performance, and RGS will be significantly (p<0.05) lower in fallers compared to their non-falling peers.

4.0 METHODOLOGY

4.1 Participant Recruitment

Female participants aged 60 and above were recruited from the Saskatoon cohort of the longitudinal Canadian Multi-centre Osteoporosis Study (CaMos). The CaMos began in 1996 with a randomized sample of men and women within a 50km radius of the Saskatoon Area. Detailed description of the CaMos recruitment methodology is available elsewhere (Kreiger N, et al. 1999), but in short, households in Saskatoon were randomly contacted using telephone listings wherein only one eligible participant per home was randomly asked to participate.

Eligible CaMos participants (N = 336) were initially mailed a letter from the Saskatoon CaMos Coordinator on behalf of the University of Saskatchewan. A letter (Appendix A) was sent to inform them of the proposed local CaMos Falls Subproject and request for their consent to be contacted by researchers at University of Saskatchewan (U of S). Return envelopes to the Saskatoon CaMos Centre were provided, and upon receiving consent the phone numbers and mailing addresses of interested women were released to the U of S. The Saskatoon CaMos Coordinator followed up with any participant who failed to return their letter. I then called each of the consenting women to schedule an appointment with our laboratory. Appointment confirmation letters and maps of campus (Appendix B) were mailed from the College of Kinesiology to each participant prior to their appointment date, and reminder calls were made the day

before to confirm attendance. Parking costs and taxi fares incurred by the participants were covered for the duration of their appointment.

4.2 Lab Protocol, Measurements and Outcomes

Upon arrival each participant was required to read and sign our consent form (Appendix C) prior to any further involvement. Assistance with the consent form was provided on an "as needed" basis to ensure full comprehension of the study details. The original CaMos identification numbers were used to distinguish each participant in our data. Following the informed consent process, a retrospective 12-month fall survey was conducted (Appendix D). The results of this brief questionnaire were later used to categorize individuals into groups based on their retrospective fall history. The primary outcome of this investigation is pQCT derived lower leg muscle density. We also investigated lower leg muscle cross sectional area, as well as lower body (TUG) and an estimate of overall muscle function (RGS). I collected all anthropometric and pQCT measures. Trained research assistants conducted the TUG test and RGS measurements. To control for physical confounders in our group comparison, and better characterize our participants we collected measures of height and weight to calculate Body Mass Index (BMI). The detailed methodology for each of these measures is described below.

4.2.1 12-Month Retrospective Falls History

Fall status was obtained using a brief questionnaire (Appendix D) which asked participants if they had fallen in the previous 12 months, and if yes, the number of times they had experienced a fall. A “fall” was broadly defined according to the Prevention of Falls Network Europe Consensus, which states “a fall is any event where any part of your body unexpectedly contacted the ground or another lower surface” (Lamb, Jørstad-Stein et al. 2005). Participants were provided with the additional option of “unsure” to control for persons with memory deficits. Fallers were classified as anyone having one or more falls, whereas non-fallers did not report a fall event during the last 12 months.

4.2.2 Anthropometric Measures

Height was measured using a wall-mounted stadiometer (Holtain Ltd.) accurate to ± 1 mm and weight (in slacks and a t-shirt) from a calibrated scale (Toledo Ltd.) accurate to ± 0.1 kg. Body Mass Index (BMI kg/m^2) was derived from height and weight values and was included in the analysis for its demonstrated ability to influence CT derived muscle attenuation (Goodpaster, Carlson et al. 2001). Tibia length was measured from the base of the medial malleolus to the superior margin of the medial epicondyle (ISAK 2001). All measures were repeated three times, and the median value was recorded.

4.2.3 pQCT Derived Muscle Density & MCSA

pQCT scans were acquired on the non-dominant leg, determined by handedness. A detailed description of participant positioning in the scanner can be found in the pQCT Measurement Protocol (Appendix E). Tomographic slices were collected at the 66% tibia (66% of the total length proximal from the distal end of tibia) using an XCT 2000 device (Stratec Medizintechnik GmbH). This site was chosen because it was demonstrated to be the location of both the greatest muscle girth and least amount of variability in size between individuals (Rittweger, Beller et al. 2000). Muscle tissue is obtained from the pQCT analysis by defining voxels with a density greater than 40 mg/mm^3 (differentiating from subcutaneous fat) but less than 280 mg/mm^3 (differentiating from bone). MD is determined by dividing the total muscle content by MCSA, and slice thickness (g/mm). Blinded to group allocation, I manually reviewed and analyzed each scan using the XCT2000 software, version 6.0 (Stratec Medizintechnik GmbH).

4.2.4 Timed Up and Go Test

To perform this test, participants were asked to stand up from a seated position in a chair, walk three meters at their normal walking pace and then return to the chair at the same pace and sit back down. During the test participants were able to make use of the chair arm rests to stand and or sit, as well as any walking aids they would normally use in their daily lives. The duration of the test was timed using a stopwatch from the command “GO” to the moment they returned and sat back into the backrest of the chair. Each participant was granted a practice trial to

ensure they understood the test protocol, followed by 3 timed trials with short rest intervals in between. If any of the trials appeared to be performed at an unusually quick pace the score was rejected, the trial repeated, and the participant was reminded that the TUG test was not a race. All TUG measurements were not blinded, collected accurate to ± 0.1 seconds with the best time score recorded.

4.2.5 Isometric Handgrip Strength

Participants underwent maximal Isometric Handgrip testing in their non-dominant hand using a JAMAR Handgrip Dynamometer (Patterson Medical Products Inc.) accurate to ± 0.1 kg according to the American Society of Hand Therapists recommendations (Fess 1992). Each participant was seated, with their shoulders adducted, elbows flexed at 90 degrees and forearms in neutral (Fess 1992; Bohannon, Peolsson et al. 2006). Three, 3-second long maximal attempts occurred with a half minute break provided between attempts. All isometric handgrip strength measures were collected with the highest score accurate to ± 1 kilogram recorded. Each participant's result was then divided by their body mass to obtain their Relative Grip Strength per kilogram of body mass (Rantanen, Era et al. 1994).

4.3 Statistics

Participants were categorized and analyzed as fallers and non-fallers based upon their 12-month retrospective fall recall responses.

4.3.1 Power Calculation

Power was calculated using data from the InChianti Study which indicated that a sample size of 43 participants per group would be necessary to detect differences in pQCT derived lower leg muscle density with a power of 80% and an alpha of 0.05 (Cesari, Leeuwenburgh et al. 2006). While this power calculation was based on a comparison of frail and non-frail men and women, frail persons are considered to have an increased fall risk. While the number of fallers currently participating in the CaMos was unknown, I anticipated that achieving a level of recruitment commensurate with this power calculation was possible given that roughly 9% of female Saskatoon CaMos participants reported falls at the 1995 baseline (Langsetmo, Hanley et al. 2008), and these same women have since aged.

4.3.2 Data Screening

All variables were screened prior to analysis for violations of normality using Z_{Skew} and $Z_{Kurtosis}$, calculated by dividing the skewness and kurtosis values by their respective standard error values. Any variable with a Z_{Skew} or $Z_{Kurtosis}$ value in excess of ± 2 was then further explored for transformation consideration using practices described by Tabachnick & Fidell (2006). If it was not possible to achieve normality through transformation, then the data for each violation was explored for the potential removal of outliers to correct any discrepancies (Tabachnick & Fidell 2006).

4.3.3 Statistical Comparison

Once all the data was screened for violations of normality, age, height, weight, and BMI were compared using independent t-tests for covariate consideration. If any covariates were identified, an analysis of covariance (ANCOVA) was used to compare lower leg MD, MCSA, TUG test scores, and RGS between the groups. If no covariates were found independent t-tests were used to analyze the group means. In addition to parametric comparisons, the non-parametric Mann-Whitney U test was utilized to compare and confirm the results of variables that violate normality. Levene's Test ($\alpha = 0.05$) was used to assess the equality of variances between groups. If variances were significantly different, the results of the adjusted comparison (where equal variances were not assumed) were reported. Mean differences were reported with 95% Confidence Intervals (CI). In the event that a data transformation was necessary, the raw value means and standard deviations were provided in a table. All statistical comparisons were performed using SPSS version 18.0 (SPSS Inc., Chicago, Ill.).

5.0 Results

5.1 Participant Recruitment

A total of 171 females agreed to have their contact information released, of which 143 women (74.2 yr SD 7.8) agreed to participate in the study at the College of Kinesiology between July and August of 2010. A small number the participants were either removed or had incomplete data due to issues with their pQCT leg scans or fall recall survey. A total of 135 women were completely analyzed. A detailed description of the participants excluded during the recruitment process and data analysis is provided in **Figure 5.1.**

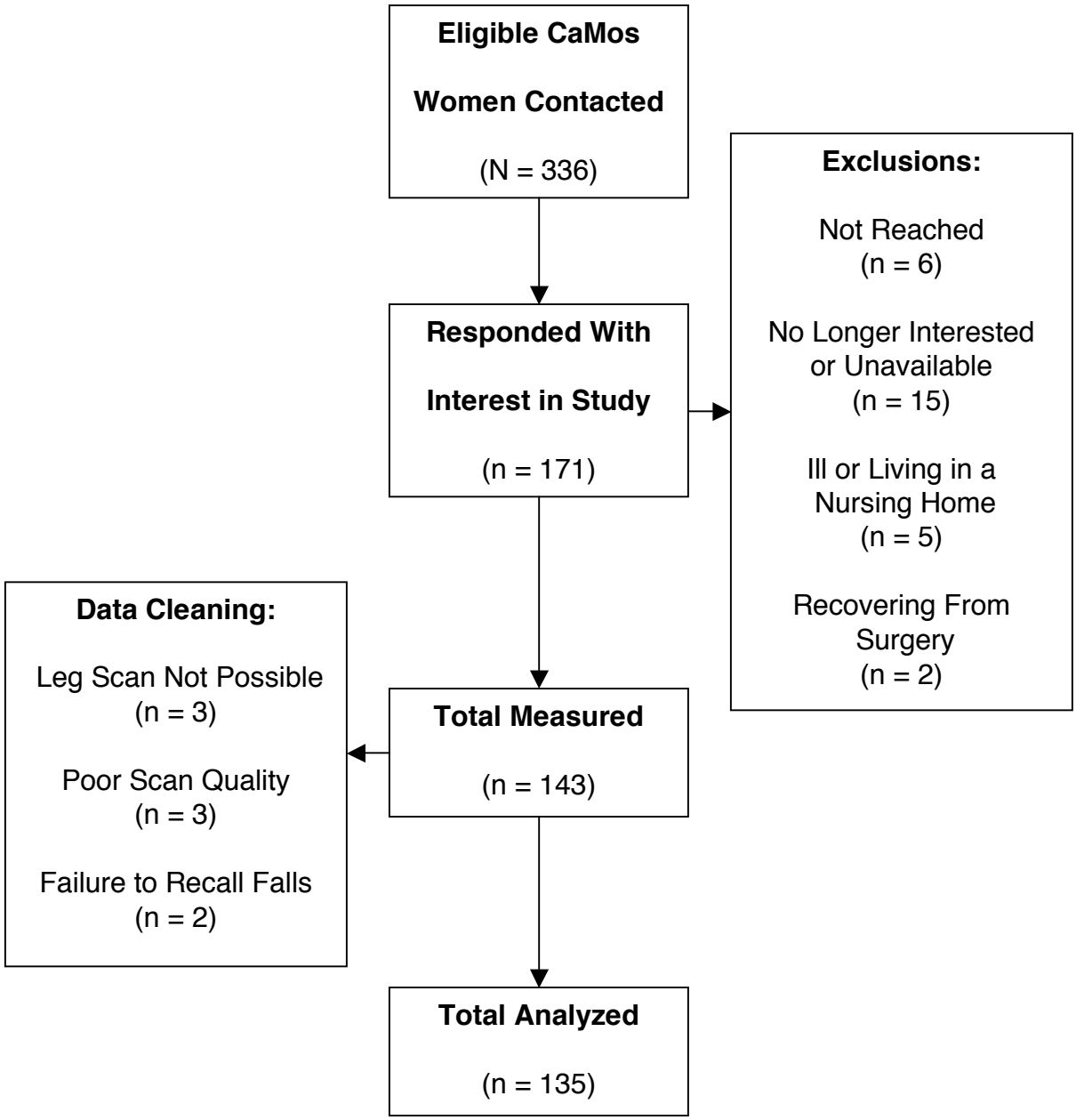


Figure 5.1: Flow chart demonstrating the participant recruitment and data analysis processes. The number of participants excluded and the reasons for their exclusion are provided.

5.2 Data Screening Results

The descriptor variables (age, height, & BMI) were normally distributed in both groups. Weight was positively skewed in the non-faller group, therefore weight was square root transformed to achieve normality (Appendix F).

In the dependent variable analysis, MD and TUG were found to be in violation of normality. The MD values of both the fallers and non-fallers were negatively skewed and therefore the MD variable was transformed using a reflection and square root technique to successfully achieve normality in both groups (Appendix F). The TUG scores of the fallers were positively skewed, and non-fallers were positively skewed and kurtotic. Logarithmic transformation was unable to correct for the TUG violations of normality in the non-faller group, therefore two outliers were removed one at a time until the logarithmic results were suitable for parametric analysis (Appendix F).

5.3 Analysis Results

When categorized as either a faller or a non-faller the participants were split 36 and 99 respectively. Age, height, weight and BMI did not significantly differ between the groups (**Table 5.1**). Therefore use of ANCOVA was unnecessary and independent t-tests were used to compare all variables between the two groups. Results of the analysis are reported as raw scores in **Table 5.2**, and the transformed 95% CI's for MD, MCSA, TUG, and RGS are displayed in **Figure**

5.2. Levene's test for homogeneity of variances was significant for TUG, therefore the results of an adjusted t-test were reported where the equality of variances was not assumed. MCSA, and RGS did not significantly differ between

	Faller		Non-Faller		
	N	Mean ± SD	N	Mean ± SD	Independent t-test *P*-Value
Age (yrs)	36	73.6 ± 8.3	99	74.3 ± 7.4	0.639
Height (cm)	36	157.8 ± 6.1	99	158.7 ± 5.6	0.392
Weight (kg)	36	70.8 ± 13.5	99	68.3 ± 12.2	0.393*
BMI (kg/m^2)	36	28.5 ± 5.5	99	27.2 ± 4.5	0.176

* *P*-value is from transformed results.

Table 5.1: Untransformed values for the descriptor variables age, height, weight and body mass index (BMI), in the faller vs non-faller comparison. No differences existed between the two groups.

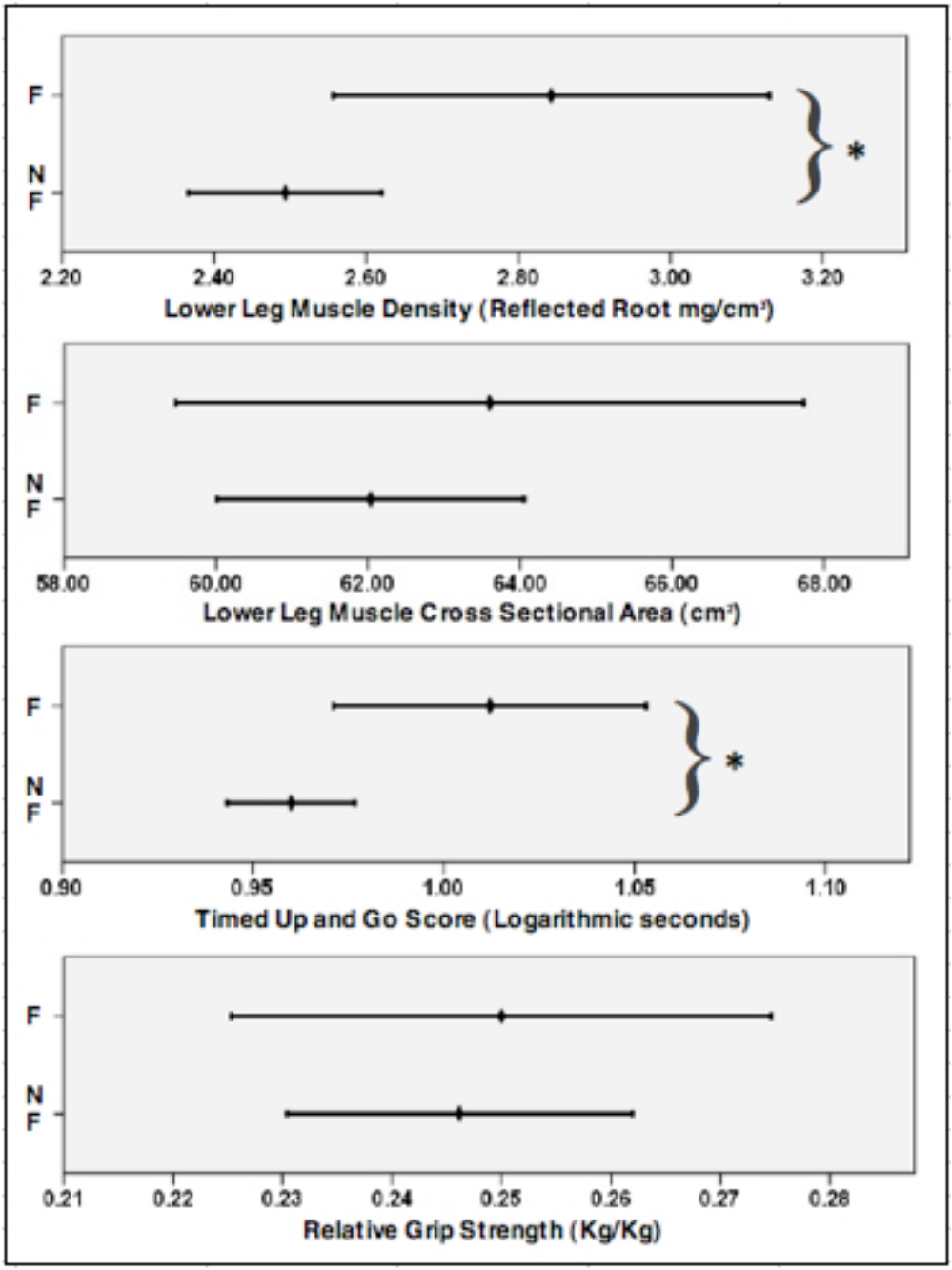
faller and non-faller groups, however MD and TUG score were lower in the Fallers ($P = 0.011$ and $P = 0.021$ respectively). Mann-Whitney U testing confirmed MD and TUG results at $\alpha = 0.05$, and 0.10 respectively (Appendix F).

	Faller		Non-Faller		% Difference Between Fallers & Non-Fallers	
	N	Mean ± SD	N	Mean ± SD		*P*-Value
MD (mg/cm^3)	36	66.5 ± 5.3	99	68.7 ± 3.2	-3.2 % (14%)	0.011*
MCSA (cm^2)	36	63.6 ± 12.2	99	62.0 ± 10.1	2.5%	0.454
TUG (s)	36	10.7 ± 3.3	97[a]	9.3 ± 1.9	15.1% (5%)	0.021*
RGS (kg/kg)	36	0.25 ± 0.07	99	0.25 ± 0.08	~ 0.0%	0.800

* *P*-values are for transformed results.

[a] Two outliers removed from TUG non-fallers.

Table 5.2: Untransformed values for age, body mass index (BMI), muscle density (MD), muscle cross-sectional area (MCSA), timed up and go score (TUG), relative grip strength (RGS) in the faller vs non-faller comparison. Transformed percent differences between the two groups appear in brackets. Due to reflection, greater transformed MD values indicate a lower MD (g/cm^3).



*$p < 0.05$

Figure 5.2: 95% Confidence Intervals for Fallers (F) and Non-Fallers (NF). Due to statistical reflection, greater reflected root lower leg muscle density values indicate a lower muscle tissue density (g/cm^3).

6.0 DISCUSSION AND CONCLUSIONS

6.1 Discussion

The objective of this study was to determine whether there were any significant differences in pQCT derived lower leg MD, MCSA, TUG, or RGS between groups of community dwelling older female fallers and non-fallers. It was hypothesized that the faller group would demonstrate significantly lower MD, MCSA, slower TUG performance, as well as smaller RGS values when compared to their non-falling peers.

This study provides novel insight into the muscle composition of elderly women who do and do not experience falls. We found a significant difference in mean lower leg MD, yet no significant differences in pQCT derived muscle size (MCSA). Fallers and non-fallers did not differ with respect to age, BMI, or RGS, but fallers were significantly slower when performing the TUG. Both groups were close to or within the range of normal values for healthy older adults for both TUG and RGS. For my TUG results Fallers (10.7s) were close to, and non-fallers (9.3s) within the expected 95% CI (8.2s - 10.2s) for adults aged 70-79 (Bohannon 2006). My result of a mean grip of approximated 17.5kg and a mean age of 74 years is almost within the normative female values for women aged 70-74, and within the normative 95% CI (14.7 – 18.1kg) for women over 75 (Bohannon, Peolsson, et al 2006). These findings suggest that my sample groups were representative of the normal healthy elderly female population.

Falls are complex multi-factorial outcomes often exacerbated by muscular deficits (Rubenstein & Josephson 2002). As far as I know, to date no other studies have examined MD (of any muscle) directly in relation to fall history in either women or men. However, there is some indirect evidence that reduced MD may be apparent in fallers. Lower muscle density/attenuation is associated with the development of mobility impairments (Visser, Kritchevsky, et al. 2002) and has been demonstrated in frail persons (Cesari, Leeuwenburgh, et al. 2006) as well as hip fracture victims (Lang, Koyama et al. 2008; Lang, Cauley et al 2010).

Using similar methodology and tools, the InChianti Study demonstrated that pQCT derived lower leg MD and a MCSA ratio (muscle area to total leg cross-sectional area) were reduced ($P < 0.05$) in frail Italian men and women when compared to their non-frail peers (Cesari, Leeuwenburgh, et al. 2006). While frailty is certainly a different categorical definition, the frailty criteria used by these researchers demonstrated predictive validity for falls, hospitalizations, disability and death (Fried, Tangen, et al. 2001). The frail subjects appear to be older than our participants; however their analyses of MD and MCSA ratio were adjusted for age, sex, and a number of co-morbidities (Cesari, Leeuwenburgh, et al. 2006).

While our pQCT MD results are in agreement with the InChianti study, we did not show a significant difference in MCSA between fallers and non-fallers. There are several plausible explanations for this. Foremost, the MCSA variable used by the InChianti study is a ratio of the total lower leg area occupied by

muscle, whereas our MCSA values are defined as the absolute muscle area (cm^2). Secondly, the InChianti study compared the MCSA ratio between frail and non-frail participants. These two groups may share some attributes with fallers and non-fallers, however they are not synonymous. Given the different measures collected it is not possible to make a comparison between our participants and the Italians in the InChianti study. It has been suggested that MCSA may not directly account for plantar flexor and dorsiflexor muscle torque in older adults (Lauretani, Russo, et al. 2003; Runge, Rittweger et al. 2004), as muscles are known to contain greater amounts of non-contractile tissues with age (Reeves, Narici, Maganaris, 2006). Therefore it is plausible that MCSA may lead to an overestimation of muscle function (Reeves, Narici, Maganaris 2006). Considering our result of lower MD, but not MCSA in fallers, our data supports this contention. It is possible that the MCSA ratio results observed in the InChianti study reflect the ability of the frailty phenotype utilized by Cesari et al. to identify a more severe stage of degeneration where gross discrepancies in the muscle can be observed by MCSA. It must also be mentioned that our study was not designed for an adequately powered comparison of MCSA, and it is likely that the MCSA effect size is too small for our sample to assess. However, a recent American report of 3,011 men and women aged 70 to 80 suggests that MCSA may not be a worthwhile variable to pursue with respect to falls and related health outcomes (Cawthorn, Fox et al. 2009). Weak strength, poor function and low muscle attenuation were all reported to be associated with a greater risk of

hospitalization in this large elderly sample, but thigh MCSA was not (Cawthorn, Fox et al. 2009). Falls account for 61.6% of all non-fatal hospital emergency room visits made by elderly Americans (Center for Disease Control (CDC) 2003).

An important finding of this study was a significantly diminished lower leg MD, and TUG performance in fallers compared to non-fallers. These results share some additional similarities with the frailty results of the InChianti Study. Walking speed is considered a key component of the TUG test and is correlated with test performance ($r = 0.66$) (Lin, Hwang, et al. 2004). Unadjusted logistic regression models revealed significant relationships between low walking speed and a 1 standard deviation increase in pQCT derived MD (OR 0.65 [0.54 - 0.79]) and relative MCSA (OR 0.80 [0.64 - 1.01]) (Lauretani, Russo 2003). However, relative MCSA was no longer significant after covariate adjustment indicating that the relationship between lower leg MCSA and poor mobility may be weak (Lauretani, Russo 2003). In concordance with this, our lower leg MCSA results did not differ between fallers and non-fallers, despite non-fallers demonstrating a significantly faster TUG test performance. Our TUG results are in agreement with previously reported results in fallers and non-fallers (O'Brien, Culham, Pickles 1997; Gunter, White, et al. 2000). This was to be expected as TUG test times are considered to be a reliable and simple screening tool for evaluating balance, lower body functional performance, and identifying fall prone individuals (Gunter, White et al 2000; Shumway-Cook, Brauer et al. 2000; Whitney, Lord, et al. 2005).

There was no difference in RGS between fallers and non-fallers. Both groups generated a grip force commensurate to ¼ of their body mass. Given previous reports of moderately strong correlations between hand-grip strength and a number of different lower body muscle performance measures (Rantanen, Era et al. 1994; Lauretani, Russo et al. 2003; Pijnappels, van der Burg et al 2008) a lower relative grip strength value was expected in fallers. There is evidence in the literature supporting handgrip strength is a predictor of falls, disability, frailty and mobility limitation (Warburton, Gledhill et al 2001b; Moreland, Richardson et al. 2004; Bohannon 2008; Pijnappels, van der Burg et al 2008; Salinen, Stenhold et al. 2010). However, it has been suggested that these predictions best apply to frail adults (Salinen, Stenhold et al. 2010). Thus, the reported relative handgrip strength as a measure of functional performance in community-dwelling persons needs to be interpreted with caution.

In this study, a faller was classified as anyone who reported one or more fall events during the last 12 months. It has been suggested that persons who experience a single fall may have done so by chance, whereas experiencing more than one fall event (multiple falls) may reflect neurological or musculoskeletal deficiencies (Nevitt, Cummings et al. 1989). This assertion is also supported by Lord, Ward et al. (1994) who demonstrated that a number of physiological test measures (including ankle and thigh strength) did not differ between single fallers and non-fallers in community dwelling women. Instead, it was demonstrated that multiple fallers (2 or more recorded falls within 12

months) performed significantly worse than both fallers and non-fallers (Lord, Ward et al. 1994). In consideration of the findings by Lord, Ward, et al. some researchers define recurrent falling as more than three falls and fallers as having 2 or more falls (Masud & Morris 2001). However, the retrospective fall recall methodology utilized in my study is not recommended for identifying multiple fallers (Peel 2000). In a slightly younger (mean age 69 yrs) sample, 12-month retrospective fall recall was reported to be less than 50% for the accurate recalll of two falls, and less than 20% for three or more (Peel 2000). Furthermore, given the 12% prevalence of multiple falls (O'Loughlin, Robitaille et al. 1993), large sample sizes are necessary to power these investigations (Sanders, Hayles et al. 2009). Therefore this study was not designed to compare multiple fallers, despite reports of lower leg musculoskeletal deficits among this population group (Lord, Ward et al. 1994). However, research concerning the importance of multiple falls in community dwelling persons is not conclusive. A study by Gunter et al. found one-time fallers to be similar to multiple fallers across a number of physical performance variables. Fallers and multiple fallers were similar in lower extremity strength and power as well as measures of functional mobility and balance (Gunter, White, et al. 2000).

It was demonstrated that a group of community-dwelling fallers present lower leg muscle density and poorer lower body functional performance compared to their non-falling peers. Muscle density reflects the attenuation of muscle, which has been validated as a measure of muscle adiposity

(Goodpaster, Kelley et al. 2000; Larson-meyer, Smith et al. 2006). The physiological mechanisms which lead to an increase in storage of muscular fat are not well understood. Cross-sectional studies report that intramuscular fat is associated with diabetes, insulin resistance, and obesity (Miljkovic, Wang et al. 2008; Kuk, Saunders, et al. 2009; Miljkovic & Zmuda 2010; Marcus, Addison et al. 2010). These findings suggest a metabolic pathway to increased muscle adiposity. It has been postulated that an age related failure of subcutaneous fat tissue to regulate fatty acids in the blood stream may be culpable (Despres & Lemieux 2006; Kuk, Saunders, et al. 2009). However, the reported associations with anemia (reduced endurance capacity) (Cesari, Penninx et al. 2004) loss of motoneuron axons (Lauretani, bandinelli, et al. 2006), muscular strength and fitness (Goodpaster, Carlson et al. 2001; Visser, Kritchevsky, et al. 2002; Goodpaster, Chomentowski et al. 2008; Taaffe, Henwood, et al. 2009), the development of mobility impairments (Visser, Goodpaster, et al. 2005), frailty (Cesari, Leeuwenburgh et al. 2006), risk of hospital admissions -often caused by falls (CDC 2003; Cawthorn, Fox et al 2009), the incidence of hip fracture (Lang, Koyama et al. 2008; Lang, Cauley et al 2010) and now falls, suggests that a general de-conditioned state, lack of physical activity and fitness may be paramount in this phenomenon. The previously mentioned metabolic manifestations may be reflective of this state, or part of a cycle of progressive de-conditioning.

6.2 Strengths and Limitations

A major strength of this study is that it is the first to compare lower leg muscle density between community dwelling female fallers and non-fallers. This research builds upon existing fall-related pQCT and CT data in the elderly. Previous reports demonstrate lower pQCT derived muscle density in frail persons (Cesari, Leeuwenburgh, et al. 2006) and lower CT derived muscle attenuation in hip fracture patients (Lang, Koyama et al. 2008; Lang, Cauley et al 2010), as well as in association with the development of mobility impairments (Visser, Kritchevsky, et al. 2002).

Only women were recruited for this study, despite the fact that elderly men also share similar fall-related health concerns (CDC 2003). Therefore our results may not be generalized to elderly male fallers and non-fallers. Our female participants were recruited from a 14-year old random sample of the Saskatoon population. This cohort of women was once representative of the elderly women of Saskatoon (Kreiger N, et al. 1999). It is possible that after 14 years of voluntary follow-up the CaMos sample may no longer represent a randomized sample of Saskatoon's community dwelling elderly women. However, my TUG and RGS results suggest that my sample groups were representative of the normal healthy elderly female population.

This study could have benefited from a direct measure of lower leg muscle (plantar flexor & dorsiflexor) performance. Relative grip strength was included as a general gauge of overall muscle function, and the Timed Up and Go test was utilized to help gauge lower body muscle function. Relative grip strength was

convenient to collect but it must be interpreted with caution due to the prevalence of arthritis or carpal tunnel syndrome in this population (Salinen, Stenhold et al. 2010). Likewise the TUG test is limited as a measure of the lower leg muscles due to multiple factors (balance, vision, proprioception, etc.), which influence its results. Also, considering that our TUG observers were not blinded to each participant's fall questionnaire response, the results are subject to observer bias. While the TUG measure is an externally valid functional test, isolating and assessing the individual lower leg muscles would further strengthen our ability to draw conclusions regarding MD and muscle performance (Suzuki, Bean et al. 2001; Webber & Porter 2010). Furthermore our retrospective design does not allow us to determine whether the differences observed between fallers and non-fallers preceeded or followed a fall event (Moreland, Richardson, et al 2004). It is plausible that reduced function could be a reflection of an injurous fall event, or a fear of falling induced activity restriction (Tinetti, Speechley, et al. 1988; Tinetti & Williams 1998).

A reliance on retrospective fall recall is a methodological limitation of this study. A 13% underestimation of falls has been reported for 12 month restropective recall methods (Cummings, Nevitt et al. 1988), however some underestimates of fall incidence are reported to be as high as 23% and 41% (Sanders, Hayles et al. 2009; Peel 2000). Even non-fallers have some trouble remembering correctly whether or not they fell in the last 12 months; approximately 15% of non-fallers misclassify themselves in retrospective recall

(Sanders, Hayles et al. 2009; Peel 2000). Regardless of whether fall data are reported prospectively or retrospectively underestimations are likely to occur. Participant denial, pride, and the externalization of fall events influence the accuracy of self report data (Rubenstein & Josephson 2002; Sanders, Hayles et al. 2009). For our study a 12-month retrospective recall was sufficient for comparing fallers and non-fallers, but a prospective assessment with weekly or monthly follow-ups would likely provide stronger data.

6.3 Future Directions

The results of this study provided novel data regarding lower leg MD in community-dwelling female fallers when compared to non-fallers. A better understanding of the physiological characteristics of fallers is necessary for effective fall prevention research. With respect to our findings, no data currently exists for males, and any similarities or differences across the sexes should be defined. The use of prospective fall monitoring as well as direct measures of lower leg muscle performance should be encouraged. An expansion of this study in a larger sample could provide a stronger data set for a sub-group analysis of multiple-fallers.

More research is needed to better define the occurrence of low muscle density in the elderly with respect to physical fitness and health. Currently only two exercise interventions report muscle attenuation as an outcome. Preliminary results suggest a modification of muscle attenuation with changes in fitness level in the elderly. Randomized controlled trials demonstrate the efficacy of exercise interventions for fall prevention. Similar studies are needed to determine if this effect is mediated by improved muscle density. Furthermore, the precision of pQCT derived MD is only reported in young adults, however the muscle physiology of this population is not comparable to the elderly. Precision should be determined in specific elderly populations before a further broadening of this research field occurs.

6.2 Summary

In a population sample of community dwelling women, fallers presented with lower leg muscle density values and lower body functional test performance when compared to their non-falling peers. Lower leg muscle cross sectional area and relative grip strength did not differ between the groups. Muscle density may reflect the adiposity of muscle tissue. While the mechanisms responsible for increased muscle adiposity are poorly understood, emerging evidence suggests that physical activity and fitness may influence muscular adipose tissue. Muscle density may serve as a physiological marker for the assessment of muscular health and fall risk in community dwelling elderly women.

7.0 References

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APPENDICES

APPENDIX A LETTER TO CAMOS STUDY PARTICIPANTS

Saskatoon Osteoporosis Centre

CaMos
Canadian Multicentre Osteoporosis Study
Étude Canadienne multicentrique sur l'ostéoporose

<<Date>>

<<Address>>

Dear CaMos Participant,

The Canadian Multi-centre Osteoporosis Study's (CaMos) success could not have happened without your contribution.

CaMos is a very unique opportunity to study many different aspects of bone health. Researchers at the University of Saskatchewan are excited to invite you to participate in a locally run CaMos subproject that will be using advanced bone and muscle imaging to study women 60 & older who may and may not experience falls. I am sending this invitation to you on their behalf. If you decide to take part, you will be given an appointment at the University of Saskatchewan for a few simple physical tests and measures. These tests and measures are a little different from the ones you have done so far for the CaMos. The appointment will take approximately 1 hour of your time. If you agree to participate, I will release your personal contact information to the university researchers so that they may contact you for an appointment at their facility. This will be done by all the confidentiality rules approved by our ethics committee.

Attached is an information sheet about the subproject, a Release of Personal Information Consent form as well as a short questionnaire. Please return the consent and questionnaire form in the self addressed and stamped envelope provided **as soon as possible**. If we do not receive the documents through the mail we will interpret it as your agreement to be contacted by Jola Thingvold by telephone to discuss this subproject.

I will be happy to tell you more about this subproject, please feel free to call me at **933-2663**. Thank you for your continuing participation and we look forward to talking to you.

Yours sincerely,

Jolanta Thingvold
CaMos Coordinator
Saskatoon Osteoporosis Center
Suite 103 Midtown Medical Center
39 - 23rd St. E. Saskatoon SK S7K 0H6

Your id number is: <<Subject's ID>>

Dr. Saija Kontulainen
Assistant Professor
College of Kinesiology
University of Saskatchewan

Dear CaMos Participant,

You are being invited to participate in a local CaMos subproject comparing muscle and bone properties in forearm and lower leg between women who have experienced multiple falls and those who have not. Muscle and bone properties will be scanned with a medical imaging tool called peripheral Quantitative Computed Tomography (pQCT) at the University of Saskatchewan.

This information package has been sent to CaMos female participants 60 years of age and older in the Saskatoon area. Enclosed is a brief questionnaire (blue form) to determine your interest in participating as well as asking you to recall the number of times you experienced a fall or near fall event in the last 12 months.

Your participation in completing and returning this brief questionnaire would be greatly appreciated. You do not have to answer any questions you are not comfortable with. **Even if you do not wish to participate please fill in and return the green form in the postage-paid and addressed envelope so we know not to contact you regarding this University of Saskatchewan subproject.** The questionnaire information will help us recruit an equal number of women with and without a history of falls and will ensure that you are only contacted if you are interested in participating. **If you do not wish to be contacted and are unable to mail your questionnaire, please call your CaMos coordinator Jola Thingvold at 933-2663 and your name will be removed from the calling list.**

We will randomly select 100 participants who expressed their interest to participate in this study. If you agreed to participate and were among this random group of 100 women you will be contacted by phone and a visit will be arranged to the University of Saskatchewan. Participation in this local subproject is completely voluntary, and you will not be paid or compensated for your time. You may refuse to participate at any point during your involvement in this subproject. If transportation to and from our facility is a problem we will cover the cost of a taxi service to and from our location. If you wish to drive to our facility we will reimburse you the cost of 90 minutes of parking on campus. Your visit will take approximately one hour and will involve another short questionnaire, pQCT scans

of your non-dominant lower leg and forearm, limb girth measures, a simple balance test, and a handgrip strength measure.

The investigators will keep your personal information confidential. Your name will not be used at all in the study records. Instead, a special number will be used.

We thank you for your previous participation in the CaMos research project, and your consideration of our request.

Failure to return the blue consent/questionnaire form or contact your CaMos coordinator will be interpreted as an indication of your agreement to be contacted by telephone regarding your interest this subproject.

If you have further questions concerning matters related to this research, please contact:

Jola Thingvold, Saskatchewan CaMos Coordinator: (306) 933-2663 or
Saija Kontulainen, College of Kinesiology, University of Saskatchewan (306) 966-1077
Andrew Frank, College of Kinesiology, University of Saskatchewan (306) 612-3345

This study has been approved on ethical grounds by the University of Saskatchewan Biomedical Research Ethics Board on May 17th 2010. Any questions regarding your rights as a participant may be addressed to that committee through the Ethics Office (306) 966-2975.

Sincerely,

Dr. Saija Kontulainen
College of Kinesiology
University of Saskatchewan
Phone: (306) 966-1077
Email: saija.kontulainen@usask.ca

Andrew Frank B.Sc
College of Kinesiology
University of Saskatchewan
Phone: (306) 612-3345
Email: andrew.frank@usask.ca

Please return this page in the envelope provided as soon as possible.

Part I: Release of Personal Contact Information

☐ I wish to be contacted by telephone by researchers at the University of Saskatchewan for my potential participation in this local subproject.

Please provide your current telephone number here:

Phone number: _____

☐ I DO NOT wish to be contacted any further for regarding the University of Saskatchewan subproject.

APPENDIX B CONFIRMATION LETTER & MAPS

UNIVERSITY OF SASKATCHEWAN

CaMos
Canadian Multicentre Osteoporosis Study
Étude Canadienne multicentrique sur l'ostéoporose

Confirmation Letter

August 23rd, 2010

Ms. XXXXXXX
Street Address
Saskatoon SK.
Postal Code

Appointment Date: August 31st 2010 **Day**: Tuesday **Time**: 9:30am

Location: **Bone Lab Room 357**
Third Floor*, Physical Activity Complex
The University of Saskatchewan
87 Campus Drive, Saskatoon SK.
(See attached map)

***Please make use of our elevator at the main entrance off Campus Drive!**

In preparation for your visit, please read the following:

1. Please a list of all the medicines or supplements prescribed by a doctor that you have taken during the last 12 months. Also bring a list of any non-prescription calcium supplements, vitamins, or any other pills you've taken during the last year.

2. *What to wear to your appointment:*

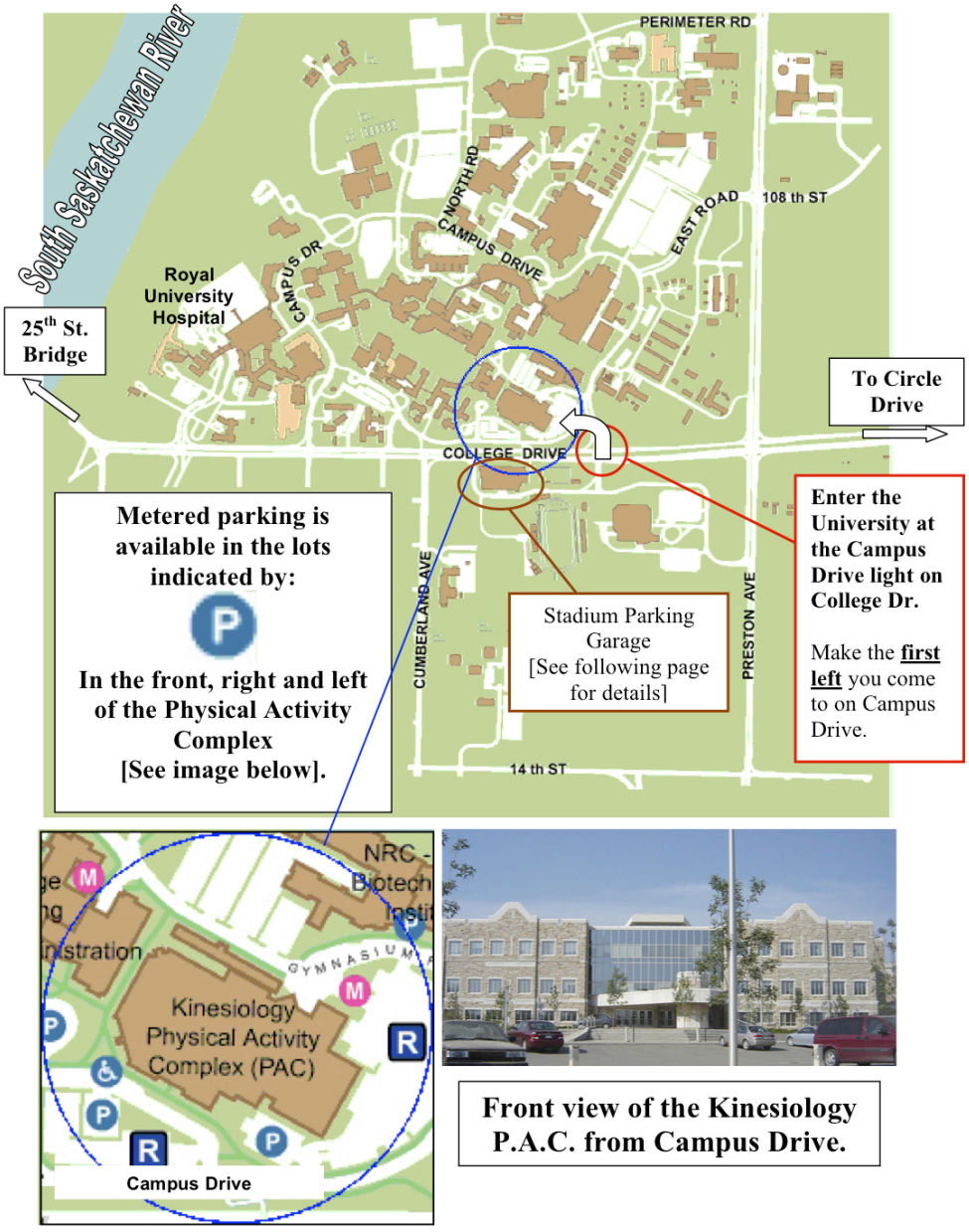
   - Wear or bring **walking shoes**, **shorts (**or slacks that can roll up past the knee) and a **short-sleeved shirt**.
   - Please **do not** wear tights, leggings, or panty hose.
   - If you need **reading glasses**, bring them with you.
   - If you need **hearing aids**, wear them and make sure they are working.
   - If you usually require a **walking aid** please bring it with you.

3. If you require a taxicab **please ask the driver for a receipt** so we can reimburse you for the travel costs. If you plan on **parking on campus** please have **$3 in change ready for the parking meters or garage** (*which we will also reimburse*).

4. *If there is a problem:*

Sometimes cancellations are unavoidable. If you are unable to make your appointment please notify the study coordinator, **Andrew Frank at (306) 612-3345**. We would appreciate as much notice as possible, so we may be able to schedule another study participant.

Location of the Physical Activity Complex (University of Saskatchewan)



<u>IMPORTANT</u>: There is a possibility that you may not be able to find a metered parking spot outside our building; If you require a parking space you are <u>guaranteed</u> to find one in the Stadium Parking Garage directly across from the Physical Activity Complex.

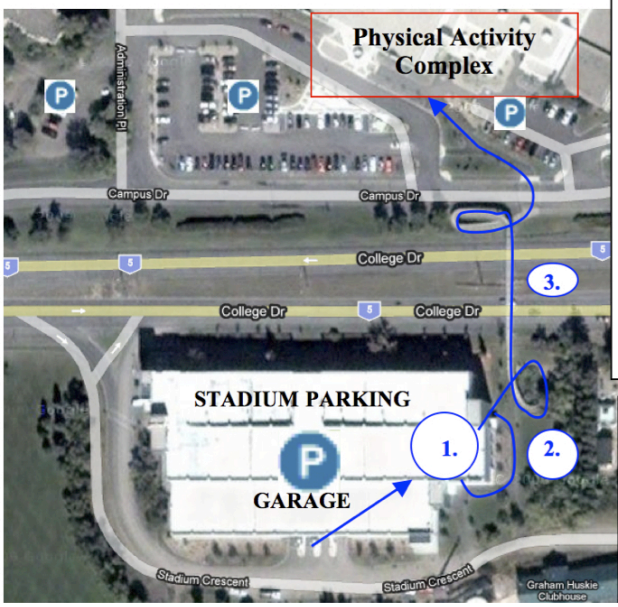
The Stadium Parking Garage can be approached 3 different ways:

1. Right off College Drive (Eastbound).

2. South on Field House Rd. off of College Drive & Keep to the right.

3. Turn onto Field House Road off of Preston Ave. & drive past the barn.

Front view of the Stadium Parking Garage from College Drive.



See our map below for a diagram of the following parking instructions.

<u>1.</u> We recommend parking on the ground level as close to the <u>EAST</u> end of the building as possible:

This will ensure your walk is shorter.

<u>2.</u> Exit the parking garage through one of the nearby east end stairwells.

<u>3.</u> Walk up the winding pathway to the pedestrian bridge that allows you to safely cross College Drive.

View of Pedestrian Walkway

APPENDIX C CONSENT FORM

Research Participant Information and Consent Form

TITLE: Do pQCT Derived Bone and Muscle Properties differ between multiple fallers and non-multiple fallers?

PROTOCOL / STUDY NUMBER: BIO: # 10-83

PRINCIPAL INVESTIGATOR: Dr. Saija Kontulainen, Assistant Professor
College of Kinesiology, University of Saskatchewan
87 Campus Drive, Saskatoon SK S7N5B2 Canada
Telephone: (306) 966-1077
Fax: (306) 966-6464
Email: saija.kontulainen@usask.ca

SUB-INVESTIGATORS: Andrew Frank [1] (MSc student); Juliegh Clark and Megan Labas [1] (undergraduate summer students); Dr. Wojciech Olszynski [2,3] & The CaMos Research Group.
[1] College of Kinesiology, U of S.
[2] College of Medicine, U of S.
[3] Saskatoon Osteoporosis Centre.

INTRODUCTION

You are invited to take part in this research because we want to learn whether or not there is a difference between the bone and muscle qualities of women who do and do not fall. We would like to test your bone density with Peripheral Quantitative Computed Tomography (pQCT), measure your muscle size, do some simple walking and grip strength testing as well as ask you do a short questionnaire.

Your participation is entirely voluntary, so it is up to you to decide whether or not you wish to take part. If you decide not to take part, you do not have to provide a reason and your decision will not affect your relationship with any of the investigators or your participation with the Canadian Multicentre Osteoporosis Study (CaMos). If you decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision.

This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand. You may ask as many questions as you need to understand what the study involves. Please feel free to discuss this with your family, friends or family physician.

STUDY PURPOSE

We will assess whether or not pQCT measurements of bone and muscle differ between women at high and low risk of falling. Falls are often responsible for both common and severe injuries experienced by older adults.

PARTICIPANTS

In order to qualify for this study you must be a female CaMos participant 60 years of age or older and live in Saskatoon or within a 50 km distance.

TIME REQUIRED TO PARTICIPATE
If you decide to participate, your visit will take about one hour of your time not including travel.

STUDY PROCEDURES

1. *First, you will be asked to complete two questionnaires regarding some background information such as your medication, fall history and your general health.*
2. *Then we will measure your height and weight along with the lengths of your non-dominant forearm and lower leg.*
3. *Your forearm will be scanned with pQCT at two sites: one scan at the wrist and one scan from the forearm. Then your lower leg will be scanned at two sites: one scan of the ankle and another one at the site that corresponds 2/3 of the leg length. A total of 4 scans will be performed.*
4. *Following the scans we will measure your arm and lower leg circumference as well as their skin fold thickness.*
5. *Next you will be asked to stand up out of a chair, walk 3 meters, turn around and return to your seat in the chair.*
6. *Finally, we will ask you to squeeze our special device as hard as you can for 3 seconds in each hand to measure your grip strength.*

BENEFITS
It's unlikely that you will personally benefit from our study. If you wish, we will give you copies of images of your scans, but because these tests are a relatively new technology, they cannot be used for diagnosing osteoporosis or related fracture risk. We hope that in the future pQCT scanning will be used in assessing fracture risk in people at a high risk of falls.

RISKS AND DISCOMFORTS
Other than walking or extending your arm and leg and holding it still for about 7 minutes, there is no significant risk or discomfort to participating in the study. There are very low amounts of radiation exposure during the pQCT scan, (an average of 2μSV), is less than what you would be exposed to by taking a return flight from Saskatoon to Toronto on a commercial airline. For comparison, the typical radiation exposure from a routine dental x-ray is 150mSV.

COST AND REIMBURSEMENTS
You will not be charged for any measurements in the study. You will not be paid for participating in this study.
If you wish, we will reimburse for;

- Parking cost on campus (up to 90 minutes, no receipt required)
- Bus/taxi fare or mileage ($0.39 per kilometre) to and from your residence and the College of Kinesiology (copy of a bus ticket, taxi receipt or a hand written receipt is required)

All of these are paid in cash and are subject to the approval of Dr. Saija Kontulainen. You will not be reimbursed for any parking or traffic violation tickets or any other unexpected costs you might incur while travelling to and from the College of Kinesiology.

CONFIDENTIALITY AND LEGAL RIGHTS

The investigators and their staff will keep the information you provide for this study confidential. Your name will not be used at all in the study records, instead, a special number (Participant ID#) will be used.

Your study records including your questionnaire and scan information will be kept for 5 years in a locked cabinet in Dr. Kontulainen's office at the College of Kinesiology. Your information and the results of the study will also be recorded in a computer database. Only the investigators will have access to your study records, and know your name. No other people or groups will have access to the data or your information. The results of this study will be presented in a scientific meeting and published in a scientific journal, but your identity will never be revealed.

By signing this document, you do not waive any of your legal rights.

VOLUNTARY WITHDRAWAL FROM THE STUDY
If you do decide to take part in this study, you are still free to withdraw at any time and without giving reasons for your decision. If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during enrolment in the study will be retained for analysis up to the point of your withdrawal.

AFTER COMPLETION OF THE STUDY
After your participation, you will be provided a summary of your bone and muscle size in comparison with the reference data. Once the study is done, if you wish, we will mail you the study findings.

CONTACT INFORMATION
If you have any questions about this study or your care/treatment or desire further information about this study before or during participation, you can contact Saija Kontulainen by emailing saija.kontulainen@usask.ca or calling (306) 966-1077.

If you have any questions about your rights as a research participant or concerns about the study, you should contact the Chair of the Biomedical Research Ethics Board, c/o the Ethics Office, University of Saskatchewan, at 306-966-4053.

This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Biomedical Research Ethics Board. The Research Ethics Board reviews human research studies. It protects the rights and welfare of the people taking part in those studies.

CONSENT TO PARTICIPATE

I have read (or someone has read to me) the information in this consent form. I understand the purpose and procedures, the possible risks and benefits of the study. I was given sufficient time to think about it. I had the opportunity to ask questions and have received satisfactory answers to all of my questions.

I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future medical care. I agree to follow the study doctor's instructions and will tell the study doctor at once if I feel I have had any unexpected or unusual symptoms.

I voluntarily consent to take part in this research study and give permission to the use and disclosure of my de-identified personal health information collected for the research purposes described above.

By signing this document I do not waive any of my legal rights. I will be given a signed copy of this consent form.

_____	_____	_____/____/____
Printed Name of Participant	Signature	Date/Month/Year

_____	_____	_____/____/____
Name of person obtaining consent	Signature	Date/Month/Year

I consent to be contacted in the future about further participation:

Yes / No (please circle one)

APPENDIX D FALL STATUS QUESTIONNAIRE

Participant ID#:_____

Fall Status Questionnaire

A "**fall**" is defined as any event where *any part of your body unexpectedly contacted the ground or another lower surface* (ie, stairs, tub, chair, etc.).

Have you fallen in the last 12 months?

☐ Yes ☐ No ☐ Unsure

If **yes:**

Have you fallen more than once? ☐ Yes ☐ No How many times? _____

APPENDIX E PQCT MEASUREMENT PROTOCOL

pQCT Measurement Protocol

- Each Participant was seated comfortably in a chair facing the pQCT gantry with their leg corresponding with their non-dominant arm positioned in the scanner.
- Legs were positioned so that each participant's popliteal fossa was resting in the leg holder attachment and a foam cushion was inserted for added comfort.
- The height of the leg holder attachment was adjusted to ensure the weight of the lower leg was not resting entirely on the pQCT gantry and the hexagonal leg clamp was closed to secure the leg below the knee.
- Each participant's foot was then secured in a plantar flexed position using the foot attachment's Velcro strap.
- Participants were then politely instructed that the scan would take approximately 4 minutes to complete, and that they were required to stay as still as possible as well as refrain from talking during the scan (to minimize movement).
- Scout scans were obtained prior to scanning and reference lines were placed at the medial tip of the distal tibia endplate.
- A single 2.3mm slice at a scan speed of 20mm/s was then acquired at a position corresponding with 66% of the total tibia length from the reference line.
- The pQCT requires daily calibration using a phantom before any measures can be done.

Figure E.1: A participant comfortably seated for pQCT scanning of their leg. Foot pronated and secured with Velcro, popliteal fossa supported by foam pad and leg elevated and clamped for maximum support and minimal movement.

APPENDIX F SPSS 18.0 RESULTS

Data Screening Results:

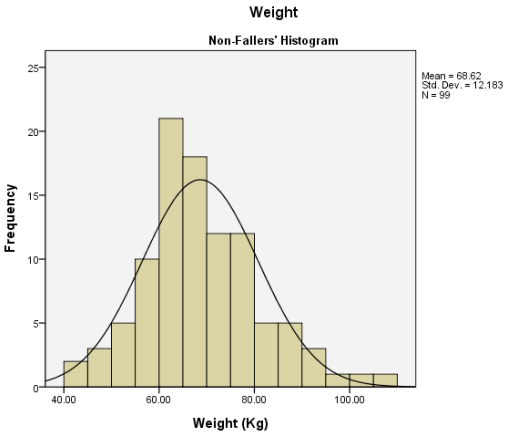
Overall Means and Standard Deviations

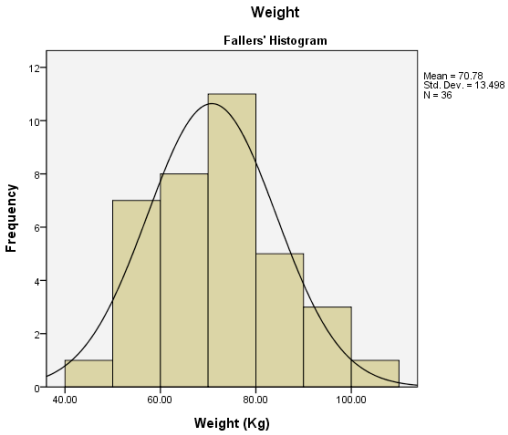
	Age	Height	Weight	BMI	MD	MCSA	TUG	RGS
N Valid	135	135	135	135	135	135	135	135
Missing	0	0	0	0	0	0	0	0
Mean	74.10	158.4674	69.1963	27.5556	68.0733	62.4504	9.8230	.2472
Std. Deviation	7.632	5.73258	12.53177	4.76811	3.99144	10.68727	2.67849	.07729

Descriptive Variable Data Screening

Descriptive Variable Statistics

Fall Status			Age	Height	Weight	BMI
Non-Fallers	N	Valid	99	99	99	99
		Missing	0	0	0	0
	Mean		74.28	158.7232	68.6212	27.2202
	Std. Deviation		7.409	5.60945	12.18252	4.47733
	Skewness		-.003	.069	.600	.358
	Std. Error of Skewness		.243	.243	.243	.243
	Z_{skew}		-0.012	0.2839	**2.469**	1.473
	Kurtosis		-.919	-.203	.829	.035
	Std. Error of Kurtosis		.481	.481	.481	.481
	Z_{kurt}		-1.911	-0.422	1.723	0.073
Fallers	N	Valid	36	36	36	36
		Missing	0	0	0	0
	Mean		73.58	157.7639	70.7778	28.4778
	Std. Deviation		8.303	6.08423	13.49785	5.45151
	Skewness		-.021	-.577	.470	.490
	Std. Error of Skewness		.393	.393	.393	.393
	Z_{skew}		-0.053	-1.468	1.196	1.247
	Kurtosis		-.838	.609	-.242	-.299
	Std. Error of Kurtosis		.768	.768	.768	.768
	Z_{kurt}		-1.091	0.793	-0.315	-0.389





Transformations:

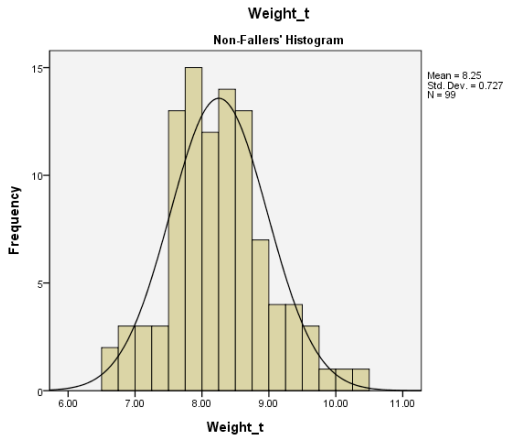
Weight is Positively skewed, therefore I square root the values to transform the Weight data (Weight_t).

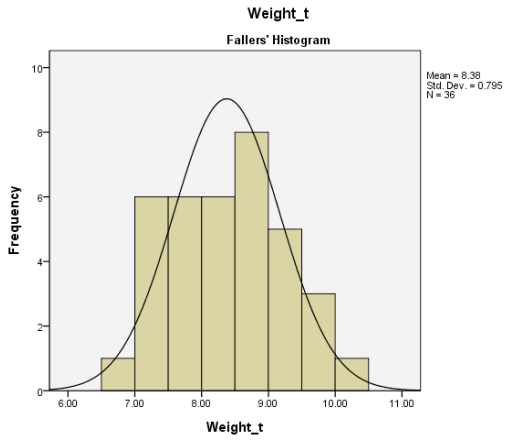
Weight_t= SQRT(Weight)

Transformed Descriptive Variable Statistics

Weight_t

Non-Faller	N	Valid	99
		Missing	0
	Mean		8.2521
	Std. Deviation		.72720
	Skewness		.299
	Std. Error of Skewness		.243
	Z_{skew}		1.230
	Kurtosis		.438
	Std. Error of Kurtosis		.481
	Z_{kurt}		0.911
Faller	N	Valid	36
		Missing	0
	Mean		8.3764
	Std. Deviation		.79482
	Skewness		.273
	Std. Error of Skewness		.393
	Z_{skew}		0.695
	Kurtosis		-.492
	Std. Error of Kurtosis		.768
	Z_{kurt}		-0.641



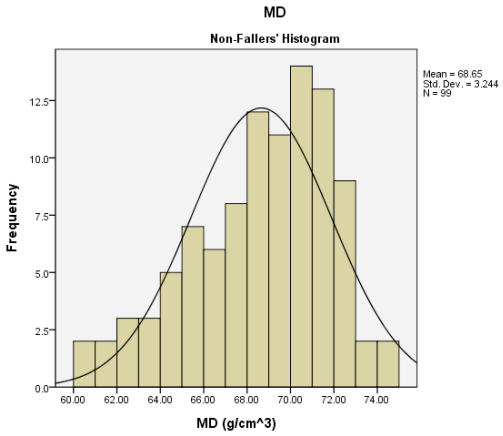


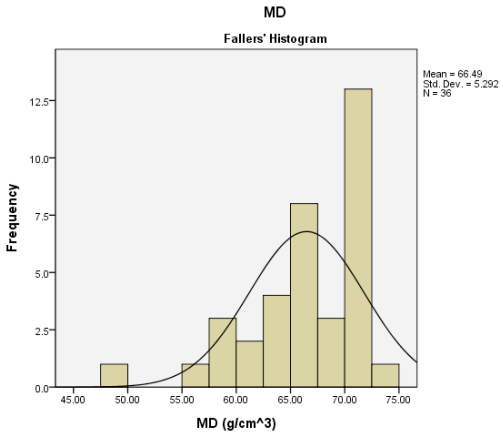
Normality of all Descriptive Variables achieved.

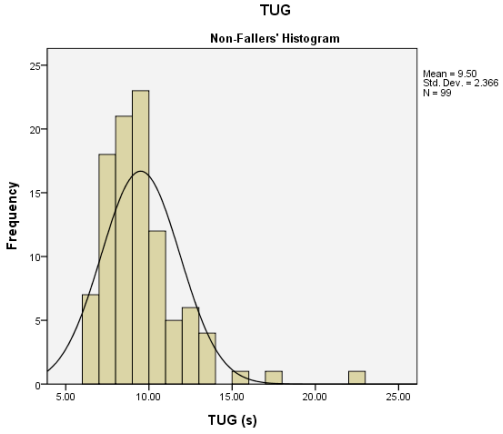
Dependent Variable Data Screening

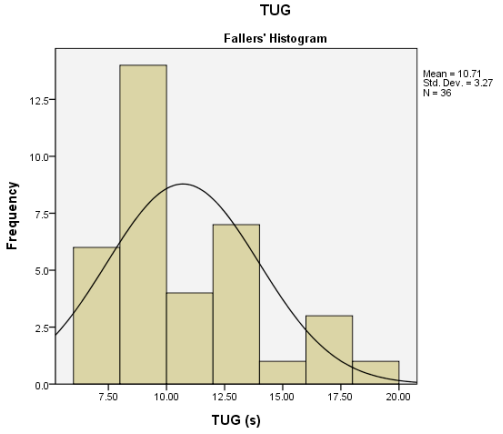
Dependent Variable Statistics

Fall Status			MD	MCSA	TUG	RGS
Non-Fallers	N	Valid	99	99	99	99
		Missing	0	0	0	0
	Mean		68.6496	62.0334	9.5010	.2462
	Std. Deviation		3.24390	10.11166	2.36624	.07915
	Skewness		-.615	.393	2.128	.251
	Std. Error of Skewness		.243	.243	.243	.243
	Z_{skew}		**-2.531**	1.617	**8.757**	1.033
	Kurtosis		-.188	-.381	7.819	.414
	Std. Error of Kurtosis		.481	.481	.481	.481
	Z_{kurt}		-0.391	-0.792	**16.256**	0.861
Fallers	N	Valid	36	36	36	36
		Missing	0	0	0	0
	Mean		66.4886	63.5969	10.7083	.2500
	Std. Deviation		5.29234	12.21307	3.26963	.07294
	Skewness		-1.268	-.576	1.152	.040
	Std. Error of Skewness		.393	.393	.393	.393
	Z_{skew}		**-3.226**	-1.466	**2.931**	0.102
	Kurtosis		1.657	.406	.714	-.128
	Std. Error of Kurtosis		.768	.768	.768	.768
	Z_{kurt}		**2.158**	0.529	0.930	-0.167









Transformations:

Transforming data for skewness usually correct kurtotic distributions as well (Tabachnick & Fidell 2006).

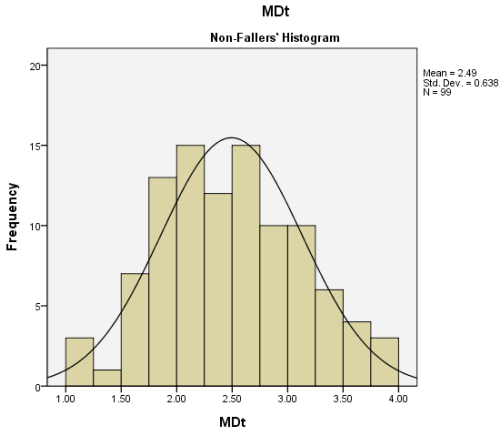
MD is negatively skewed, therefore I reflect and square root the values to transform the MD data (MDt).

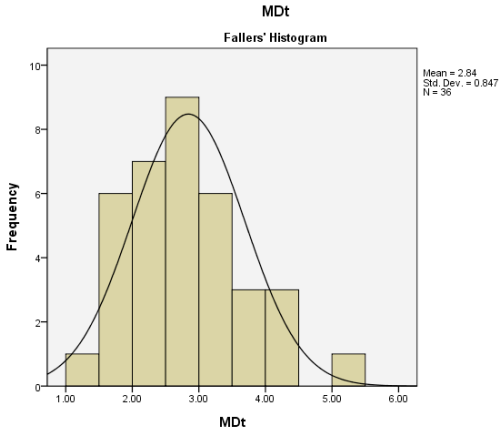
MDt = SQRT(K-MD), where K is a constant equal to the largest MD value +1.

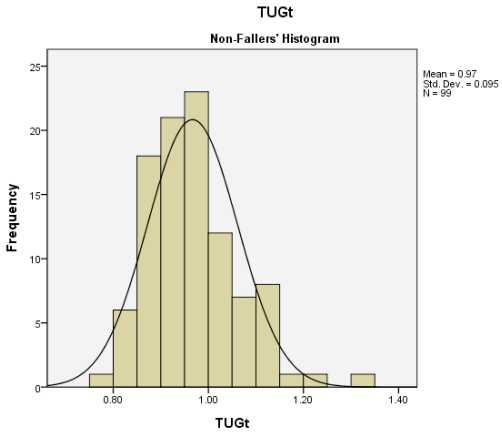
TUG is Positively skewed, therefore I “Log 10” the values to transform the TUG data (TUGt).

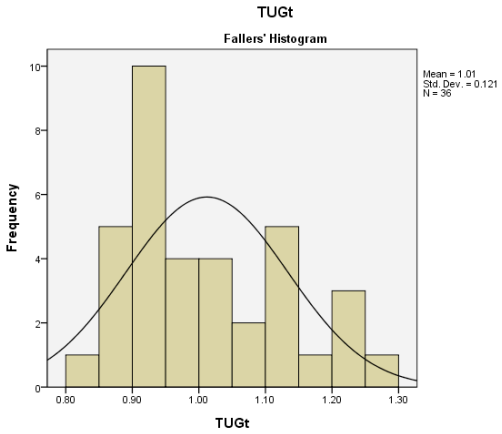
TUGt = LG10(TUG)

Transformed Results:









Transformed Dependent Variable Statistics

Fall Status			MDt	TUGt
Non-Fallers	N	Valid	99	99
		Missing	0	0
	Mean		2.4935	.9667
	Std. Deviation		.63796	.09477
	Skewness		.060	.945
	Std. Error of Skewness		.243	.243
	Z_{skew}		0.247	**3.889**
	Kurtosis		-.448	1.860
	Std. Error of Kurtosis		.481	.481
	Z_{kurt}		-0.931	**3.867**
Fallers	N	Valid	36	36
		Missing	0	0
	Mean		2.8433	1.0121
	Std. Deviation		.84725	.12126
	Skewness		.591	.650
	Std. Error of Skewness		.393	.393
	Z_{skew}		1.504	1.654
	Kurtosis		.088	-.425
	Std. Error of Kurtosis		.768	.768
	Z_{kurt}		0.115	-0.553

Transformation of TUG failed to produce normality → Data examined for outliers.

*Removal of outlier SK04360: TUGt =1.34, 3.9 SD from the non-faller mean (5.3 SD from the raw non-faller TUG mean)

Transformed Dependent Variable Statistics

(SK04360 Removed)

TUGt

Non-Fallers	N	Valid	98
		Missing	1
	Mean		.9629
	Std. Deviation		.08731
	Skewness		.533
	Std. Error of Skewness		.244
	Z_{skew}		**2.184**
	Kurtosis		.277
	Std. Error of Kurtosis		.483
	Z_{kurt}		0.573
Fallers	N	Valid	36
		Missing	0
	Mean		1.0121
	Std. Deviation		.12126
	Skewness		.650
	Std. Error of Skewness		.393
	Z_{skew}		1.654
	Kurtosis		-.425
	Std. Error of Kurtosis		.768
	Z_{kurt}		-.343

Removal of TUG/TUGt outlier furthest from the mean failed to produce normality.

→ Data examined for additional outliers.

*Additional removal of outlier SK03963: TUGt = 1.24; 2.9 SD from the non-faller mean, (3.3 SD from the raw non-faller TUG mean).

Transformed Dependent Variable Statistics

(SK04360 & SK03963 Removed)

TUGt

Non-Fallers	N	Valid	97
		Missing	2
	Mean		.9600
	Std. Deviation		.08303
	Skewness		.336
	Std. Error of Skewness		.245
	Z_{skew}		1.371
	Kurtosis		-.263
	Std. Error of Kurtosis		.485
	Z_{kurt}		-.542
Fallers	N	Valid	36
		Missing	0
	Mean		1.0121
	Std. Deviation		.12126
	Skewness		.650
	Std. Error of Skewness		.393
	Z_{skew}		1.654
	Kurtosis		-.425
	Std. Error of Kurtosis		.768
	Z_{kurt}		-.553

Normality of all Dependent Variables achieved. Data screening complete.

Data Analysis Results:

Descriptive Variables Analysis

Descriptive Variable Group Statistics (Weight Transformed)

	FS10	N	Mean	Std. Deviation	Std. Error Mean
Age	Fallers	36	73.58	8.303	1.384
	Non-Fallers	99	74.28	7.409	.745
Height	Fallers	36	157.7639	6.08423	1.01404
	Non-Fallers	99	158.7232	5.60945	.56377
Weight_t	Fallers	36	8.3764	.79482	.13247
	Non-Fallers	99	8.2521	.72720	.07309
BMI	Fallers	36	28.4778	5.45151	.90858
	Non-Fallers	99	27.2202	4.47733	.44999

No descriptive variables significantly differed between the faller and non-fallers.

Therefore no covariates need to be considered, and ANCOVA is unnecessary.

Descriptive Variable Analysis: Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Age	Equal variances assumed	.515	.474	-.470	133	.639	-.699	1.490	-3.646	2.247
	Equal variances not assumed			-.445	56.514	.658	-.699	1.571	-3.847	2.448
Height	Equal variances assumed	.289	.592	-.859	133	.392	-.95934	1.11680	-3.16832	1.24963
	Equal variances not assumed			-.827	58.002	.412	-.95934	1.16022	-3.28177	1.36309
Weight_t	Equal variances assumed	.943	.333	.856	133	.393	.12424	.14511	-.16279	.41126
	Equal variances not assumed			.821	57.643	.415	.12424	.15129	-.17865	.42712
BMI	Equal variances assumed	1.694	.195	1.359	133	.176	1.25758	.92507	-.57218	3.08733
	Equal variances not assumed			1.240	53.134	.220	1.25758	1.01391	-.77595	3.29110

Dependent Variable Analysis

Dependent Variable Group Statistics (MD and TUG Transformed)

	FS10	N	Mean	Std. Deviation	Std. Error Mean
MDt	Fallers	36	2.8433	.84725	.14121
	Non-Fallers	99	2.4935	.63796	.06412
MCSA	Fallers	36	63.5969	12.21307	2.03551
	Non-Fallers	99	62.0334	10.11166	1.01626
TUGt	Fallers	36	1.0121	.12126	.02021
	Non-Fallers	*** 97	.9600	.08303	.00843
RGS	Fallers	36	.2500	.07294	.01216
	Non-Fallers	99	.2462	.07915	.00795

MD and TUG Raw Values

Fall Status			MD	TUG
Non-Faller	N	Valid	99	97
		Missing ***	0	2
	Mean		68.6496	9.2918
	Std. Error of Mean		.32602	.18751
	Std. Deviation		3.24390	1.84677
Faller	N	Valid	36	36
		Missing	0	0
	Mean		66.4886	10.7083
	Std. Error of Mean		.88206	.54494
	Std. Deviation		5.29234	3.26963

*** The TUG scores for 2 participants (Subject ID's SK04360, SK03963) in the non-faller group were excluded (See Data Screening Results for Justification).

Dependent Variable Analysis: Independent Samples t-Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
MDt	Equal variances assumed	3.330	.070	2.570	133	**.011**	.34976	.13607	.08062	.61890
	Equal variances not assumed			2.255	50.159	.029	.34976	.15508	.03829	.66123
MCSA	Equal variances assumed	.949	.332	.750	133	.454	1.56351	2.08341	-2.55739	5.68441
	Equal variances not assumed			.687	53.437	.495	1.56351	2.27510	-2.99890	6.12592
TUGt	Equal variances assumed	10.532	**.001**	2.815	131	.006	.05207	.01849	.01548	.08865
	Equal variances not assumed			2.378	47.713	**.021**	.05207	.02190	.00803	.09610
RGS	Equal variances assumed	.141	.708	.254	133	.800	.00384	.01510	-.02602	.03370
	Equal variances not assumed			.264	67.004	.792	.00384	.01453	-.02516	.03284

Non-Parametric Comparisons:

MD Ranked 1 (lowest) through 135 (highest)

Weight Ranked 1 (lowest) through 135 (highest)

TUG Ranked 1 (fastest) through 135 (slowest)

Non-Parametric Statistics

Fall Status			Rank of MD	Rank of Weight	Rank of TUG
Non-Faller	N	Valid	99	99	99
		Missing	0	0	0
	Mean		73.56566	66.72222	65.16667
Faller	N	Valid	36	36	36
		Missing	0	0	0
	Mean		57.94444	72.76389	78.20833

Mann-Whitney U Test Results:

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Rank of MD1 is the same across categories of FS10.	Independent-Samples Mann-Whitney U Test	.044	Reject the null hypothesis.
2	The distribution of Rank of Weight is the same across categories of FS10.	Independent-Samples Mann-Whitney U Test	.436	Retain the null hypothesis.
3	The distribution of Rank of TUG is the same across categories of FS10.	Independent-Samples Mann-Whitney U Test	.095	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

APPENDIX G ETHICS CERTIFICATION

Certificate of Completion

This is to certify that

Andrew William Frank

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has completed the Interagency Advisory Panel on Research Ethics'
Introductory Tutorial for the
Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)

Issued On: April-24-2009

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Saija Kontulainen	Kinesiology	10-83

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
College of Kinesiology
87 Campus Drive
Saskatoon SK S7N 5B2

STUDENT RESEARCHERS
Juliegh Clark, Andrew Frank, Megan Labas

SPONSORING AGENCIES
UNIVERSITY OF SASKATCHEWAN

TITLE: Do pQCT Derived Muscle Cross Sectional Area and Muscle Density Differ Between Multiple Fallers and Non-Multiple Fallers?

ORIGINAL REVIEW DATE	APPROVED ON	APPROVAL OF	EXPIRY DATE
06-May-2010	17-May-2010	Researcher's summary (10-May-2010) (15-Mar-2010) Research Participant Information and Consent Form(15-May-2010) Appendix B Fall, Medication History, Limb Dominance and Activity Questionnaire Appendix C RAND SF-36 Questionnaire Instrument Letter to Participant (1) Letter to Participant (2) Short questionnaire confirmation letter	16-May-2011

Delegated Review: ☒ Full Board Meeting: ☐

CERTIFICATION
The study is acceptable on scientific and ethical grounds. The Bio-REB considered the requirements of section 29 under the Health Information Protection Act (HIPA) and is satisfied that this study meets the privacy considerations outlined therein. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research projects involving human subjects under section 29 of The Health Information Protection Act (HIPA).

Gordon McKay, Ph.D., Vice-Chair
University of Saskatchewan
Biomedical Research Ethics Board

Please send all correspondence to:

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1607 – 110 Gymnasium Place
Saskatoon, SK Canada S7N 4J8